Janssen Scientific Affairs*

Clinical Protocol

Efficacy and Safety of Rivaroxaban Prophylaxis Compared with Placebo in Ambulatory Cancer Patients Initiating Systemic Cancer Therapy and at High Risk for Venous Thromboembolism

Protocol BAY59-7939/39039039STM4001/18262 Phase 3b
AMENDMENT-4

JNJ39039039/BAY59-7939 (Rivaroxaban)

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

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

EudraCT NUMBER: 2015-001630-21

Status: Approved
Date: 16 February 2018
Prepared by: Janssen Scientific Affairs, LLC
EDMS number: EDMS-ERI-102610148: 6.0

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

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PROTOCOL AMENDMENTS

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Amendment-4	16 February 2018

Amendments below are listed beginning with the most recent amendment.

Amendment-4 (16 February 2018)

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

The overall reason for the amendment: The overall reason for the amendment is to include lower extremity symptomatic distal deep venous thrombosis (DVT) in the composite primary efficacy endpoint and individual composite secondary efficacy endpoint as these events are clinically important and can lead to proximal DVT and/or pulmonary embolism (PE) in cancer patients, and to indicate that towards the end of the enrollment phase, approximately 800 subjects were planned to be randomized into the study due to the high subject discontinuation rate.

Applicable Section(s)	Description of Change(s)
Rationale: Symptomatic lower extremity distal DVT was included in the composite primary efficacy endpoint and composite secondary efficacy endpoint as these events are clinically important and can lead to proximal DVT and/or PE.	
Synopsis Objectives and Hypothesis, Efficacy Evaluations, Statistical Methods 2.1. Objectives; 2.2. Hypothesis; 3.2. Study Design Rationale; 9.2.1. Efficacy Evaluations and Outcomes; 9.2.2. Efficacy Endpoints; 11.5. Efficacy and Safety Analyses; Attachment 1: Reporting of Efficacy Endpoints, Adverse Events, and Serious Adverse Events	Added symptomatic lower extremity distal DVT to the composite primary efficacy endpoint and composite secondary efficacy endpoint, and where applicable, deleted it as an individual component from other secondary efficacy endpoints.

Applicable Section(s)	Description of Change(s)
Rationale: Due to the high subject discontinuation rate, additional subjects were planned to be randomized into the study towards the end of the enrollment phase.	
Synopsis Overview of Study Design, Statistical Methods; 3.1. Overview of Study Design; 11.2. Sample Size Determination	Specified that towards the end of the enrollment phase, approximately 800 subjects were planned to be randomized into the study due to the high subject discontinuation rate.
Rationale: Clarifications were made to the statistical analyses methods and corrections were made to the efficacy evaluations/outcomes and endpoints.	
Synopsis Statistical Methods; 11.5. Efficacy and Safety Analyses; 11.5.1. Safety Endpoints, Laboratory, and Vital Signs Data Analysis	Deleted pooling of data across both strata from the primary efficacy composite endpoint analysis. Added that the Cox's proportional hazards model will be stratified for the primary safety endpoint of time to a major bleeding event.
9.2.1. Efficacy Evaluations and Outcomes; 9.2.2. Efficacy Endpoints	Symptomatic proximal upper extremity DVT was corrected to symptomatic upper extremity DVT and non-fatal PE was corrected to symptomatic non-fatal PE.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical and formatting changes were made.

Amendment-3 (18 July 2016)

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

The overall reason for the amendment: The overall reason for the amendment is to provide further clarifications and ensure consistency within the protocol. Modifications include, but are not limited to, changes to allow for the rescreening of subjects, the removal of the requirement related to the use of a double-barrier method of birth control, the correction of the physical description of the study drug, and an update to the adverse event (AE) and serious adverse event (SAE) collection and reporting requirements.

Applicable Section(s)	Description of Change(s)
Rationale: Symptomatic lower extremity distal deep vein thrombosis (DVT) has been added to the secondary objectives and evaluations.	
Synopsis, Secondary Objectives; Synopsis, Efficacy Evaluations; 2.1. Objectives (Secondary Objectives); 9.2.1. Efficacy Evaluations and Outcomes; 9.2.2. Efficacy Endpoints	Revised the secondary efficacy objectives and evaluations to include the evaluation of the individual components of the primary efficacy composite variable, (ie, confirmed fatal/non-fatal arterial thromboembolism [ATE] events, confirmed fatal/non-fatal visceral venous thromboembolism [VTE] events, symptomatic lower extremity distal DVT, a composite of symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic upper extremity DVT, symptomatic non-fatal pulmonary embolism (PE), incidental PE, and all-cause mortality, and a composite of symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, and VTE-related deaths).
Rationale: Clarification has been provided regarding the rate of stratification.	
Synopsis, Overview of Study Design; 3.1, Overview of Study Design; 11.2. Sample Size Determination	Made minor text changes to clarify the rate of stratification.
Rationale: Clarification has been provided regarding the date of randomization.	
Synopsis, Overview of Study Design; Time and Events Schedule; 3.1. Overview of Study Design; 5. Treatment Allocation and Blinding (Randomization Procedures); 9.1.3. Double-Blind Treatment Phase (Day 1/Day of Randomization)	Made changes to clarify that the date of randomization is considered the date that the subject is assigned to study drug in the Interactive Web Response System (IWRS) while Day 1 is considered the date that the study drug is initiated.
Rationale: Clarification has been provided regarding the visit window for the duration of treatment during the double-blind treatment period.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design Throughout the protocol	Made changes to clarify that subjects will be instructed to take the study drug for a fixed duration of 180 days (±3 days). Removed references to visit windows when specifically associated with study visits on Day 180 and Day 210.
Rationale: Modifications have been made to clarify the role of the Clinical Endpoint Committee (CEC) and the events to be adjudicated.	
Synopsis, Overview of Study Design; Synopsis, Efficacy Evaluations; Synopsis, Statistical Methods (Efficacy and Safety Analyses); 3.1. Overview of Study Design; 3.2. Study Design Rationale (Choice of Efficacy Outcome/ Endpoint); 9.1.3. Double-Blind	Made changes to specify that the CEC is blinded, to provide additional details regarding the purpose of the CEC, and to provide consistency regarding the events that will be adjudicated, including all routine compression ultrasounds.

Applicable Section(s)	Description of Change(s)
Treatment Phase (Double-Blind Treatment Period [Day 1-Day 180]); 9.2.1. Efficacy Evaluations and Outcomes; 9.2.1.1. Definitions; 9.2.2. Efficacy Endpoints; 9.4.1. Bleeding Events; 11.2. Sample Size Determination; 11.5. Efficacy and Safety Analyses; 11.9.3. Clinical Endpoint Committee; 12.4.1. All Adverse Events	
Rationale: Modifications have been made to clarify the role of the Independent Data Monitoring Committee (IDMC) and the information that it will review.	
Synopsis, Overview of Study Design; Synopsis, Statistical Methods (Interim Analysis); 3.1. Overview of Study Design; 5. Treatment Allocation and Blinding (Unblinding); 11.4. Interim Analysis; 11.9.2. Independent Data Monitoring Committee; 12. Adverse Event Reporting	Made changes to specify that the IDMC is unblinded and that it will periodically assess the safety of subjects and evaluate efficacy.
Rationale: An option to allow for the rescreening of subjects has been added.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 9.1.2. Screening Phase	Added text indicating that subjects may be rescreened once and specified that screening procedures must be repeated if rescreening is performed after the initial 2-week screening period.
Rationale: Modifications have been provided to clarify that chemotherapy does not have to last for ≥6 months for the subject to be eligible; however, the intent to treat for 6 months is required.	
Synopsis, Dosage and Administration; 4.1. Inclusion Criteria (Criterion 6); 6. Dosage and Administration	Added text indicating that systemic cancer therapy will be initiated within ±1 week of receiving the first dose of study drug, with the intention of receiving the systemic cancer therapy during the double-blind treatment period for a duration determined by the treating oncologist according to standard protocols of clinical care.
Rationale: Further clarification has been provided to explain that temporary drug interruptions can lead to permanent discontinuation if >14 days.	
Synopsis, Dosage and Administration; (Interruption of Study Drug); 8. Prestudy and Concomitant Therapy (Prohibited Therapy); 10.2.1. Temporary Interruption of Study	Added text indicating that subjects who miss >14 consecutive days of study drug will need to permanently discontinue the study drug. In Section 10.2.1, Temporary Interruption of Study Treatment, included the list of prohibited therapies that will lead to temporary interruption of the study drug instead of including a cross reference to Section 8, Prestudy and Concomitant Therapy.

Applicable Section(s)	Description of Change(s)
Treatment; 10.2.2. Permanent Discontinuation of Study Treatment	
Rationale: Definition of the per-protocol population has been clarified.	
Synopsis, Statistical Methods (Study Population/Analysis Sets)	Added text to define the per-protocol population as a subset of the intent-to-treat (ITT) population, with the condition that subjects with major protocol deviations will be excluded from the per-protocol population.
Rationale: Clarification has been provided regarding the analysis of the key secondary efficacy endpoints.	
Synopsis, Statistical Methods (Primary Efficacy Composite Endpoint Analysis); 11.5. Efficacy and Safety Analyses	Added text to explain that key secondary efficacy endpoints will be analyzed in a similar fashion as the primary efficacy endpoint.
Rationale: Clarification has been provided regarding the use of historical laboratory data	
Time and Events Schedule; 9.1.2. Screening Phase; 9.4.2.2. Clinical Laboratory Tests	Removed references to local laboratories to clarify that historical standard-of-care laboratory results may be used during the screening visit to determine subject eligibility.
Rationale: Use of the Modification of Diet in Renal Disease formula has been included to determine adequate renal function.	
Time and Events Schedule; 4.1. Inclusion Criteria Attachment 5 Attachment 6	Added text indicating that creatinine clearance (CrCl) can be calculated using the Cockcroft-Gault formula or the Modification of Diet in Renal Disease formula. The Modification of Diet in Renal Disease formula has been provided. The CKD-EPI equation for estimating eGFR has been provided.
Rationale: Text added to clarify that isolated distal DVT events will not be included in the primary efficacy outcome due to controversy regarding overall clinical significance.	
3.2. Study Design Rationale (Rationale for Mandatory Bilateral Lower Extremity Venous Compression Ultrasonography)	Specified that the primary efficacy outcome will not include isolated distal DVT events.
Rationale: A revision to the standard inclusion criterion relating to the use of double-barrier contraception has been made for rivaroxaban.	
4.1. Inclusion Criteria (Criteria 8 and 10); 4.3. Prohibitions and Restrictions (Criterion 2)	Revised text regarding appropriate and adequate methods of birth control for men.
Rationale: A revision was made for consistency with other sections of the protocol	
4.1. Inclusion Criteria (Criterion 1)	Added qualifier that subjects must be ambulatory men and women.
Rationale: A revision was made to align the inclusion criterion with the language in the informed consent form (ICF).	
4.1. Inclusion Criteria (Criterion 10)	Modified text regarding male contraception to align with the ICF.

Applicable Section(s)	Description of Change(s)
Rationale: Examples of P2Y12 inhibitors have been added for clarity.	
4.2. Exclusion Criteria (Criterion 13)	Added clopidogrel, prasugrel, and ticagrelor as examples of P2Y12 inhibitors.
Rationale: Compression stockings are permitted regardless of the setting	
4.3. Prohibitions and Restrictions (Criterion 3)	Added text to indicate that compression stocking may be used during the course of the study.
Rationale: Clarification has been provided to ensure that subjects do not stop taking the study drug if using an inhibitor as this will result in decreased concentrations of the study drug.	
8. Prestudy and Concomitant Therapy (Prohibited Therapy)	Deleted reference to combined P-glycoprotein (P-gp) and strong cytochrome P450 (CYP) 3A4 inducers from the list of prohibited medications and added it to the list of therapies to be avoided during the study.
Rationale: Thromboprophylaxis with mechanical devices is prohibited because they could potentially interfere with the efficacy assessments.	
8. Prestudy and Concomitant Therapy (Prohibited Therapy)	Moved the criterion from the list of prohibited therapies and qualified the reason for prohibition.
Rationale: Modifications have been made to clarify DVT locations.	
9.2.1.1. Definitions	Definitions have been updated regarding DVT location.
Rationale: The sections related to biomarkers were consolidated to minimize duplication.	
9.3. Biomarkers	Duplicate section was deleted and text moved to Section 9.5.1, Evaluations.
Rationale: Modifications have been made to clarify that clinically significant bleeding events include both major and relevant non-major bleeding events	
9.4.1.1. Management of Study Drug for Bleeding Events	Added text specifying that the study drug should be stopped or the subject managed per the guidelines for both major and relevant non-major clinically significant bleeding events.
Rationale: Tympanic temperature readings may be used in the study.	
9.4.2.3. Vital Signs	Tympanic temperature has been added to the list of vital signs measurements.
Rationale: Modifications to the subject completion definitions have been provided to specify that subjects who discontinue the study drug should remain in the study and continue the study visits, if possible, regardless of the reason for discontinuation and to ensure consistency throughout the protocol.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 10.1. Completion; 10.2.2. Permanent Discontinuation of Study Treatment	Made changes to the definitions for completion of the double-blind treatment period, completion of the study, and not completing the study. Removed the definition for completion of the treatment period to avoid duplication with the definition for completion of the double-blind treatment period. Clarified that subjects who permanently discontinue the study should complete an unscheduled end-of-treatment (EOT) visit as soon as possible from the time that the study drug was discontinued and that subjects will required to complete all remaining study visits and procedures, including the Day 180/EOT and Day 210/end-of-study (EOS) visits.
Rationale: The physical description of the study drug is not correct for this study.	
14.1. Physical Description of Study Drug(s)	Made changes to correct the physical description of the study drug.
Rationale: Modifications have been made for consistency with the SAP.	
11.1. Analysis Populations and Observation Periods	The subject population has been updated to include all randomized subjects instead of those with a valid informed consent.

Applicable Section(s)	Description of Change(s)
11.5. Efficacy and Safety Analyses	Key subgroups have been modified.
Rationale: Minor modifications have been made to clarify the initial estimates of expected VTE rates.	
Synopsis, Sample Size Determination; 11.2. Sample Size Determination	Changes were made to clarify and align the text throughout the document.
Rationale: Modifications were made to clarify that at 80% power, the subpopulation sample size will need to show a somewhat larger effect size (ie, difference in incidence rates between the 2 treatment arms) to be statistically significant. For the APC group, this effect size is estimated to be at least 14%.	
11.2. Sample Size Determination	Added text specifying that the differences in incidence rates between the 2 treatment groups will be slightly larger.
Rationale: Modifications have been made to align the attribution definitions for AEs with the electronic case report form (eCRF) data capture.	
12.2.2. Attribution Definitions	Changed the term "unlikely" to "doubtful" and added definitions for "life-threatening" and "death".
Rationale: Updates have been made to the AE and SAE collection and reporting requirements given that adjudication is being performed by the CEC for outcome events.	
12.4.1. All Adverse Events	Made changes to clarify that suspected outcome events will be captured in the eCRF and will be waived from SAE collection and unblinding, and exempted from expedited reporting. Symptomatic lower extremity distal DVT was added to the list of events and it was clarified that this list also includes all bleeding events, not just those that are major and clinically relevant non-major bleeding events. Also removed the requirement to collect any non-VTE- or non-ATE-related death or non-clinically relevant bleeding event as a SAE in the eCRF.
Attachment 1, Reporting of Efficacy Endpoints, Adverse Events, and Serious Adverse Events	Table was updated.
Rationale: Text was included in the wrong section of the protocol.	
9.6.4. Pharmacokinetic Analysis; 9.7. Health Care Resource Utilization	Moved text associated with the analysis of data to Section 11, Statistical Methods.
Rationale: Updates have been made to align text in the Time and Events Schedule to the rest of the protocol.	
Time and Events Schedule (Footnotes i and j)	Reference to the Cockroft-Gault formula was removed from Footnote i and a cross reference to the CKD-EPI (Attachment 6) was made in Footnote j.
Time and Events Schedule (Footnote o)	Footnote o was deleted as it was not associated with and assessment in the table and the instructions are clearly stated in the protocol. Renumbered subsequent footnotes accordingly.
Rationale: Modifications have been made for consistency with the current version of the protocol template.	
Throughout the protocol	Template changes have been applied, as appropriate.
Rationale: Modifications have been made to correct inconsistencies in text and to remove text deleted from previous amendments.	
Throughout the protocol	Made changes to harmonize wording in sections that discuss similar topics and deleted statements that were inadvertently missed in previous amendments.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Applicable Section(s)	Description of Change(s)

Amendment-2 (16 September 2015)

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

The overall reason for the amendment: The overall reason for the amendment is to correct the physical description of the study drug being provided and to allow for flexibility in the initiation of the first dose of study drug relative to randomization with IWRS.

Applicable Section(s)	Description of Change(s)
Rationale: To allow for flexibility in the initiation of the first dose of study drug relative to randomization with IWRS, a window for starting study drug was added.	
Synopsis (Overview of Study Design); Section 3.1 Overview of Study Design; Time and Events Schedule (footnote "f"); Section 5 Treatment Allocation and Blinding (Randomization Procedures); Section 6.0 Dosage and Administration; Section 9.1.3 Double-Blind Treatment Phase (Day 1/Day of Randomization)	The following sentence has been added throughout the protocol as indicated. 'Subjects will have up to 4 days from the point of being randomly assigned study drug within IWRS to initiate their study drug treatment in order to accommodate those subjects who will be receiving their study drug from a centralized drug depot but every effort should be made to initiate study drug within 1 day.'
Rationale: The sentence in the 5th paragraph was removed as it is repeated above in that same paragraph.	
Section 3.1 Overview of Study Design	The last sentence in the paragraph was removed, 'Imaging from routine care (eg, CT scans ordered primarily for staging or restaging of malignancy) will be adjudicated for asymptomatic PE or DVT events'.
Rationale: To correct the physical description of the study drug that is actually being provided for this study	
Section 14.1 Physical Description	The following sentence has been added. 'The study drug supplied for this study is rivaroxaban 10 mg and matching placebo, provided as round, light red tablets. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.' The following sentences have been deleted 'The rivaroxaban supplied for this study are the tablet formulations containing 10 mg of active drug. The round, light red, tablets will be over-encapsulated in size 00 capsule shells. The tablets are immediate release dosage forms with rapid dissolution characteristics under in vitro test conditions. Each tablet contains the active ingredient rivaroxaban and the excipients; croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, hypromellose, and sodium lauryl sulfate. The tablets are film-coated with hypromellose, macrogol, and titanium dioxide/ ferric oxide red.'
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
Rationale: Correction of error in biomarker sampling timing.	
Synopsis (Biomarker Evaluations)	Blood samples will be collected from subjects at Screening ~~Randomization~~, Weeks 8 and 16 visits and Day 180/EOT to measure levels of circulating D-dimer, P-selectin, and Tissue Factor.

Amendment-1 (31 August 2015)

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

The overall reason for the amendment: The overall reason for the amendment is to include time-to-event analyses and additional protocol recommendations based on regulatory authority input.

Applicable Section(s)	Description of Change(s)
Rationale: Inclusion of time-to-event analyses based on regulatory authority input for the primary efficacy composite endpoint.	
Synopsis; Section 3.2 Study Design Rationale; Section 9.2.2 Efficacy Endpoints; Section 11 Statistical Methods; Section 11.5 Efficacy and Safety Analyses	This analysis will be performed on a time-to-first-event basis during the observation period up to Day 180 (±3 days), using a stratified Cox proportional hazard model (stratification factor: advanced pancreatic cancer [APC] or non-APC) including treatment group as a categorical exploratory variable with 2 levels (ie, rivaroxaban, placebo) and include the pooled data across both strata based on the Intent-to-treat [ITT] analysis set.
Rationale: Input received from the regulatory authorities to include methodology of handling of missing data**.**	
Section 11.3 Handling of Missing Data	Addition of Section
Rationale: Input received from regulatory authorities to increase the sample size.	
Synopsis (Overview of Study Design, Sample Size Determination), Section 3.1 Overview of Study Design, Section 11.2 Sample Size Determination	The sample size was increased from 625 to 700 subjects.
Rationale: Input received from the regulatory authorities concerning biomarker evaluation.	
Synopsis (Exploratory Objectives, Biomarker Evaluations, Time and Events Schedule, footnote m); Section 2.1 Objectives; Section 9.5.1 Evaluations	Netosis (NETs) was deleted and Tissue Factor was added.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of the role of the local imaging laboratory. Compression ultrasonography examinations will be assessed at a local imaging laboratory by a site designated radiologist. All diagnostic imaging for all events will be done locally and adjudication will be centralized.	
Synopsis (Overview of Study Design) Time and Events Schedule, footnotes a and e; Section 3.1 Overview of Study Design; Section 9.1.2 Screening Phase	A local reader will be responsible to determine that an event has occurred. The Clinical Endpoints Committee (CEC) will adjudicate all events. In Overview of Study Design in Synopsis: The ~~local imaging laboratory~~ independent CEC will also assess all ultrasound examinations to ensure uniformity of asymptomatic event ascertainment.
Rationale: Timing of the Day 180/End-of-Treatment [EOT] visit window was modified to be more conducive to scheduling subjects' procedures.	
Synopsis (Overview of Study Design; Time and Events Schedule [Day 180/EOT visit]), footnotes b, k, and l, Section 3.1 Overview of Study Design, Section 10.1 Completion	Subjects will be instructed to take study drug for a fixed duration of 180 days and will then complete the Day 180/EOT Visit. The Day 180/EOT Visit will be completed within a window of ±3 days.
Rationale: Timing of the bilateral lower duplex venous compression ultrasonography at the Day 180/EOT visit was modified to be more conducive to scheduling subjects' procedures.	
Synopsis (Overview of Study Design, Time and Events Schedule footnote l); Section 3.1 Overview of Study Design, Section 9.1.3 Double-blind Treatment Phase	"The Day 180/EOT Visit will be completed within a window of ±3 days. The CU planned for the Day 180/EOT Visit must occur within this window and before the last dose of study drug. Subjects who discontinue early will have an unscheduled EOT visit and will have up to 2 days after the last dose of study drug to have the CU completed but every effort should be made to have it done as soon as possible after the last dose. A CU should not be performed at all if it is not possible to have it completed within 2 days of the last dose of study drug.
Rationale: Clarifications to exclusion criteria were made.	
Section 4.2 Exclusion Criteria	Criterion #2 was modified to known history of brain metastases; Criterion #8 was removed Previously diagnosed/treated venous thromboembolism (VTE) ≤30 days prior to randomization; Criterion # 14 (atrial fibrillation was provided for clarity as an example); Criterion #19 was removed as it was duplicated in Criterion #14
Rationale: Clarification of dual antiplatelet therapy bullet; addition of new bullet for prohibited anticoagulant therapy; clarification on modification of pre-existing therapy; prohibition of single and dual P2Y12 antagonist antiplatelet therapy due to the increased risk of bleeding	
Section 4.2 Exclusion Criteria, #13 Criterion; Section 8.0 Prestudy and Concomitant Therapy	Modification to: P2Y12 receptor antagonist antiplatelet therapy, daily nonsteroidal anti-inflammatory drugs, or other medications known to increase the risk of bleeding (a daily dose of ≤100 mg of aspirin is permitted)

Applicable Section(s)	Description of Change(s)
Rationale: Clarification on types of prestudy and concomitant therapies that will be collected was added.	
Time and Events Schedule, footnote "k"; Section 8.0 Prestudy and Concomitant Therapy	All concomitant therapies taken throughout the double-blind treatment period for the treatment of AEs/SAEs, prohibited medications, additional medications as listed in Section 8 and systemic cancer therapy and radiotherapy must be recorded in the eCRF except supplements such as fish oil, herbal medicines and vitamins. In addition, concomitant therapies should also be recorded beyond the Day 180/EOT visit only in conjunction with SAEs that meet the criteria outlined in Section 12.4.2. Serious Adverse Events.
Rationale: Language was added to add flexibility to use local laboratory tests to determine eligibility if previously drawn labs are already available during the Screening period.	
Time and Events Schedule footnote "e"	An IWRS will be used to randomly assign subjects to treatment. Randomization may be completed once clinical laboratory results and imaging results (CU) from the local reader are available to confirm subject eligibility. Note: Local laboratory results may be used for the screening visit to confirm eligibility; these results must be documented in the subjects' source documentation. In this case, subjects will be randomized on Day 1 based on the results from the local laboratory that confirms eligibility; however, screening blood samples must still be collected and sent to the central laboratory for analysis. Subsequently, if the screening results from the central laboratory are exclusionary the local laboratory results will take precedence and must be recorded in the eCRF to document eligibility.
Rationale: Language was modified to allow for standard-of-care in the event of diagnosis of a suspected DVT or PE.	
Synopsis (Overview of Study Design), Section 3.1 Overview of Study Design	If a subject has a suspected efficacy outcome event during the study, the treating physician should exercise clinical judgment and follow guidelines to apply the standard-of-care. Unblinding of study drug should not be necessary, as anticoagulation regiments do not require adjustment regardless of use of placebo vs rivaroxaban when administered in the dose used in this study. Section 9.2.3 Approach to the Subject with an Efficacy Outcome Event, was added
Rationale: Additional details provided regarding study drug discontinuation were added.	
Section 10.3 Permanent Discontinuation of Study Treatment	Subjects missing more than 14 consecutive days of taking study drug will be discontinued from further study therapy and censored for the time-to-event analyses. These subjects will not be restricted from seeking appropriate medical care available outside the protocol, but will be encouraged to make every effort to continue with their scheduled study visits until the planned end of their study duration.
Rationale: Details were provided on all-cause mortality data collection based on input received from the regulatory authorities.	
Section 9.2.1 Efficacy Evaluations and Outcomes	All-cause mortality will be recorded

Applicable Section(s)	Description of Change(s)
Rationale: Additional details were provided on the primary composite endpoint (analysis, endpoints, and objectives) based on input received from internal authorities.	
Synopsis (Primary Objectives, Hypothesis, Efficacy Evaluations, Primary Composite Endpoint Analysis); Section 9.2.1 Efficacy Evaluations and Outcomes; Section 9.2.2 Efficacy Endpoints	The primary efficacy analysis will include composite events (eg, objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE and VTE-related death) occurring from randomization up to Day 180 (+3 days) for all randomly assigned subjects in the study.
Rationale: Additional definitions to secondary endpoints were added based on regulatory input.	
Synopsis (Secondary Objectives; Efficacy Evaluations), Section 9.2.2 Efficacy Endpoints	The key secondary efficacy endpoints include symptomatic VTE events (DVT/PE), VTE-related deaths and all-cause mortality from time to randomization to Day 180 (+3 days). Other secondary efficacy objectives include the evaluation of the individual components of the primary efficacy composite variable analyzed separately, a composite of confirmed fatal/non-fatal arterial thromboembolism (ATE) events, a composite of confirmed fatal/non-fatal visceral VTE events, and a composite of symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic upper extremity DVT, non-fatal PE, incidental PE and all-cause mortality.
Rationale: Additional details were provided for the clinical events relevant to the efficacy endpoints.	
Synopsis (Overview of Study Design); Time and Events Schedule, footnote "o"; Section 9.1.1, Overview; Section 9.1.3, Double-blind Treatment Phase; Section 10.3, Permanent Discontinuation of Study Treatment	If the subject is unwilling or unable to return for any visits, or is lost-to-follow up, the investigator should collect as much follow-up information as possible for each remaining visit according to the Time and Events Schedule, including contacting the subject or legally acceptable representative by telephone or by mail to determine vital status and outcome ascertainment, as agreed to by the subject during the informed consent process. The site must document all attempts to try to contact the subject in the source documents.
Rationale: Recommendations were received from regulatory authorities to include concept of targeted safety collection and reporting of adverse events/serious adverse events as in our other sponsored studies.	
Attachment 1 (revised)	

Applicable Section(s)	Description of Change(s)
Rationale: Regulatory authorities requested a single blood draw at Week 8 to estimate exposure to rivaroxaban.	
Synopsis (Exploratory Objectives); Time and Events Schedule; Time and Events Schedule footnote n); Section 2.1 Objectives; Section 9.6 Pharmacokinetics; Section 9.6.1 Pharmacokinetic Sample Collection and Handling; Section 9.6.2 Analytical Procedures; Section 9.6.3 Pharmacokinetic Parameters; Section 9.6.4 Pharmacokinetic Analyses	These are new sections added based on the request for PK sampling.
Rationale: Health Care Resource Utilization section was added based on input received from internal subject matter experts.	
Synopsis (Exploratory Objectives); Time and Events Schedule footnote p; Section 2.1 Objectives; Section 9.7 Health Care Resource Utilization; Section 11.7 Health Care Resource Utilization	Health care resource utilization (HCRU) data will be collected as part of the endpoint assessments, at Weeks 8 and 16, and Day 180/EOT, for all patients, or until study drug discontinuation. The data collection will be specific to the study outcomes of DVT, PE, or bleeding, including visits to health care providers, hospitalization, length of hospitalization, and use of diagnostic procedures.
Rationale: Regulatory authorities made comments regarding temporary discontinuations during hospitalizations and suggested subjects remain on study drug.	
Synopsis (Interruption of Study Drug); Section 10.2.1 Temporary Interruption of Study Treatment	In case of major surgery or major bleeding risk procedure, the investigator may consider holding the prior day study dose [skip both, day before and day of surgery, doses of study drug], weighing the risk of bleeding against that of VTE. Consider bridging with parental anticoagulation if necessary. Study drug should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. Study drug should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short. The investigator may consider resuming study therapy 24 hours after achieving hemostasis for low-bleeding risk or minor surgical procedures, and at 48 hours in case of major or high-risk bleeding procedures, noting that the time to onset of therapeutic effect is short.
Rationale: Clarification on procedures for premature discontinuation was added.	
Section 10.2.1 Temporary Interruption of Study Treatment	Subjects who have a study drug interruption of >14 days must be discontinued form study drug treatment.

Applicable Section(s)	Description of Change(s)
Rationale: Additional statistical details on analyses set and periods were added.	
Section 11.1 Analysis Populations and Observation Periods	On-treatment: this observation period includes data from the first dose of study drug to 2 days after the last dose of the study drug, inclusively. For time-to-event analyses, subjects who do not experience endpoint events during this period will be censored on the last dose date +2 days or at the last day of their completed unscheduled EOT assessments for study outcomes during the treatment period whichever occurs first.
Rationale: Changes were made to include time-to-event analysis based on regulatory authority input for the main safety endpoint.	
Section 11.5.1 Safety Endpoints, Laboratory and Vital Signs Data Analysis	The main safety endpoint includes time to a major bleeding event in treated subjects in each randomized treatment group.
Rationale: Clarification on IDMC data review process was added.	
Section 11.9.2 Independent Data Monitoring Committee	The IDMC will monitor unblinded data following a charter.
Rationale: Recommendations received from regulatory authorities to remove potential outcome events.	
Section 12.2.1 Adverse Event Definitions and Classifications	Section was deleted
Rationale: Staging details were added to the Time and Events Schedule for subjects with lymphoma.	
Time and Events Schedule	Addition of Ann Arbor staging.
Rationale: The ECOG performance status and CVC status are no longer necessary at the Day 210/EOS visit.	
Time and Events Schedule	Removed ECOG performance status and CVC status at Day 210
Rationale: Coagulation testing is required at the screening visit.	
Time and Events Schedule; Section 9.1.1 Overview	Coagulation analysis (2 mL) was added to the section.
Rationale: Additional safety monitoring added to ensure that either the investigator or a qualified subinvestigator will be required to see each subject at every study visit for clinical assessment of the subject's status.	
Synopsis (Overview of Study Design); Section 3.1 Overview of Study Design; Section 9.1.3 Double-blind Treatment Phase	Either the PI or a qualified subinvestigator will be required to see each subject at every study visit for clinical assessment of the subject's status.

Applicable Section(s)	Description of Change(s)
Rationale: Request was received from regulatory authorities for inclusion of eGFR.	
Synopsis (Time and Events Schedule footnote j); Attachment 5	eGFR will be calculated using the Modification of Diet in Renal Disease formula (see Attachment 5).
Rationale: Samples will not be stored beyond 5 years.	
Section 16.2.5. Long-Term Retention of Samples for Additional Future Research	Samples collected in this study may be stored for up to 5 years (or according to local regulations) for future research and will not include molecular biological or genetic studies.
Rationale: Further clarification provided on the definitions for the different types of DVTs.	
Section 9.2.1.1 Definitions	The following definitions will be applied by the CEC based on objective confirmation. Asymptomatic lower extremity proximal DVT The presence, in subjects who are asymptomatic or otherwise unaware of and lack clinical signs for a DVT located in the proximal veins of lower extremities (proximal to the deep calf veins eg, external iliac, common femoral vein, proximal femoral vein, distal femoral vein, popliteal vein), as evidenced by a positively diagnosed and adjudicated CU. If the CU is deemed to be of unsatisfactory quality, confirmation may be done by venography if ordered by the investigator or qualified designee. Symptomatic lower extremity proximal DVT The adjudicated presence, in subjects who are symptomatic or otherwise aware of and/or have clinical signs for a DVT located in the proximal deep veins of the lower extremities (proximal to the deep calf veins, eg, external iliac, common femoral vein, proximal femoral vein, distal femoral vein, popliteal vein), as evidenced by the final clinical diagnosis including a positively adjudicated CU. If the CU is deemed to be of unsatisfactory quality, confirmation can be done by venography if ordered by the investigator or qualified designee. <u>Symptomatic Upper Extremity DVT</u> The adjudicated presence, in subjects who are symptomatic or otherwise aware of and/or have clinical signs for a DVT located in the proximal veins of the upper extremities as confirmed by abnormal CU. Note: Thrombosis of the central line will not be considered as suspicion of DVT unless the patient presents with symptoms (eg, swelling, erythema, pain, distal paresthesia, neck swelling, headache, congestion of subcutaneous collateral veins). <u>Symptomatic non-fatal PE</u> The adjudicated presence, in subjects who are symptomatic or otherwise aware of and/or have clinical signs for a PE objectively confirmed by CT scan. <u>Visceral VTE</u> Thrombi formed in portal, splenic, superior mesenteric, inferior mesenteric, hepatic, gonadal, renal veins or inferior vena cava as evidenced by CT scan.

Applicable Section(s)	Description of Change(s)
Rationale: Further defined reporting of adverse events.	
Section 12.4.1 All Adverse Events	These events include: • Symptomatic lower extremity proximal DVT • Asymptomatic lower extremity proximal DVT • Symptomatic upper extremity DVT • Symptomatic non-fatal PE • Incidental PE • VTE-related death • ATE events (eg, MI, stroke) • Visceral VTE • Major bleeding events and clinically relevant non-major bleeding events. The serious adverse events need to be reported to the sponsor within the appropriate timeline as described in Section 12.2.1, Serious Adverse Events. • Adverse events leading to permanent study drug discontinuation • All SAEs that are not considered endpoint events as listed above • While one of the outcome measures is all-cause mortality, any non-VTE or non-ATE related death will be reported as a SAE. • Non-clinically relevant bleeding events
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
Rationale: References were not used in the protocol.	
References Section	The following references were deleted: 11, 13, 14, 17, 18, 19, 26, 30, 33, 42, 45, 56, 59, and 61

SYNOPSIS

Efficacy and Safety of Rivaroxaban Prophylaxis Compared with Placebo in Ambulatory Cancer Patients Initiating Systemic Cancer Therapy and at High Risk for Venous Thromboembolism

Venous thromboembolism (VTE) is the second leading cause of death in patients with cancer. The risk of VTE is particularly high in the first few months following the diagnosis of cancer and there is an increased risk for VTE in patients initiating systemic cancer therapy and with late-stage metastatic disease. Current guidelines do not recommend the routine use of VTE prophylaxis in most ambulatory patients with cancer due to limited randomized controlled trial (RCT) data and uncertainty on the benefit/risk in the ambulatory cancer population. Rivaroxaban is a potent, orally administered and highly selective direct inhibitor of activated factor X (FXa) and has been shown to be effective in preventing VTE in patients undergoing hip/knee replacement surgery as well as reducing VTE recurrence in patients with deep vein thrombosis (DVT) and pulmonary embolism (PE). The aim of this clinical study is to evaluate the efficacy and safety of rivaroxaban versus placebo for primary thromboprophylaxis in ambulatory cancer patients at a high risk for VTE undergoing systemic cancer therapy.

OBJECTIVES AND HYPOTHESIS

Primary Objectives

The primary efficacy objective is to demonstrate that rivaroxaban is superior to placebo for reducing the risk of the primary composite outcome as defined by objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and VTE-related death in ambulatory adult subjects with various cancer types receiving systemic cancer therapy who are at high risk of developing a VTE.

Secondary Objectives

The key secondary efficacy objectives of this study are to compare the efficacy of rivaroxaban with placebo for reducing the risk of symptomatic VTE events and VTE-related deaths, and all-cause mortality in ambulatory adult subjects with various cancer types receiving systemic cancer therapy who are at high risk of developing a VTE. Other secondary efficacy objectives include the evaluation of the individual components of the primary efficacy composite variable, confirmed fatal/non-fatal arterial thromboembolism (ATE) events, confirmed fatal/non-fatal visceral VTE events, a composite of symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and all-cause mortality, and a composite of symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, and VTE-related deaths.

Safety Objectives

The primary safety objective of this study is to assess major bleeding events (as defined by the International Society on Thrombosis and Haemsotasis [ISTH]). In addition, clinically relevant non-major bleeding, minor bleeding, and any bleeding (defined as major, clinically relevant non-major, and minor bleeding) will be assessed as measured by the ISTH definition.

Exploratory Objectives

The exploratory objectives of this study are:

- To assess inflammation- and hypercoagulability-related biomarkers including D-dimer, P-selectin, and Tissue Factor
- To analyze the steady state pharmacokinetics (PK) and exposure response of rivaroxaban
- To collect health care resource utilization (HCRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this study)

Hypothesis

The primary hypothesis of this study is that prophylactic treatment with rivaroxaban administered at a dose of 10 mg once daily for up to 6 months will be superior to placebo in reducing the risk of objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and VTE-related death in ambulatory adult subjects with various cancer types receiving systemic cancer therapy who are at high risk of developing a VTE.

OVERVIEW OF STUDY DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, superiority study comparing the efficacy and safety of rivaroxaban with placebo for primary prophylaxis of VTE (defined as DVT and/or PE) in ambulatory adult men and women, 18 years of age and older, with various cancer types who are scheduled to initiate systemic cancer therapy as a component of their standard-of-care anticancer regimen, who have a baseline Khorana thromboembolic risk score of ≥2, and are judged by the investigator or qualified designee to be an appropriate candidate for treatment with either placebo or rivaroxaban for thromboprophylaxis based on their clinical status.

Initially, a target of approximately 700 subjects were to be randomly assigned into the study in a 1:1 ratio to 1 of 2 treatment groups with approximately 350 subjects per treatment group, with an assumed rate of discontinuation of approximately 20% from the study. Towards the end of the enrollment phase, approximately 800 subjects were planned to be randomized into the study due to the high subject discontinuation rate. In addition, subjects will be stratified at randomization by tumor type (advanced pancreatic cancer [APC] or non-APC); it is estimated that approximately 25% of the subjects randomly assigned are those with APC.

The study consists of 3 periods: a 2-week screening period, a 180-day double-blind treatment period with an end-of-treatment (EOT) visit, and a 30-day post-treatment follow-up period with a Day 210/end-of-study (EOS) visit. The duration of participation in the study for each subject is approximately 32 weeks.

At the screening visit (Day -14 to -1), designated study personnel will explain the nature of the study, including all relevant details, and obtain written informed consent from the subject before initiation of any study-related procedures. Once all required screening procedures are completed, qualifying laboratory results are received, and bilateral lower extremity venous duplex compression ultrasonography (CU) results are received from the local reader, subjects will be asked to return to the study site as soon as possible, but no more than 14 days after the screening visit, for the randomization (Day 1) visit. Subjects found to have baseline DVT on screening CU or incidental DVT or PE as identified from routine care imaging (eg, spiral computed tomography [CT] scans ordered primarily for staging or restaging of malignancy) within 30 days prior to randomization will not be eligible for randomization. Subjects may be rescreened once, if not randomized after the initial screening. All screening procedures must be repeated if rescreening is performed after the initial 2-week screening period.

Eligible subjects will be randomly assigned by an Interactive Web Response System (IWRS), in a 1:1 ratio to receive 1 of 2 treatments during the double-blind treatment period: rivaroxaban 10 mg orally once daily or placebo 10 mg orally once daily for a maximum of 180 days (±3 days). Subjects will be stratified at randomization by tumor type (APC or non-APC) and will be instructed to take the study drug for a fixed duration of 180 days (±3 days). Subjects will have up to 4 days to complete the Day 1 visit from the point of being randomly assigned to the study drug within IWRS (date of randomization) to initiate their study drug treatment in order to accommodate those subjects who will be receiving their study drug from a centralized drug depot; however, every effort should be made to initiate study drug within 1 day. Every effort should be made to initiate systemic cancer therapy on the same day as administration of the first dose of study drug, or within 72 hours of the first dose of study drug when at all possible. However, for pragmatic reasons, subjects may be allowed to initiate systemic cancer therapy within a period of ±1 week prior to, or after their first dose of study drug, with a preference of this occurring within the first week following study drug administration.

Subjects will have study visits, inclusive of visit windows, performed at Week 8 (±7 days), Week 16 (±7 days), and Day 180/EOT (±3 days) during the double-blind treatment period, and will undergo mandatory CU at these visits. The CU planned for the Day 180/EOT visit must occur within this window and before the last dose of study drug. Following a 30-day post-treatment follow-up period (Day 210/EOS ±7 days from randomization), all subjects (or their legally acceptable representative), including those who discontinued the study drug prior to the Day 180 visit, will be contacted by telephone for a Day 210/EOS visit follow-up assessment and will have their vital status (eg, dead, alive, or lost to follow-up) as well as clinical status review for suspected outcome and safety bleeding events completed. Adverse events (AEs) and concomitant medications will be collected.

All study visits may be coordinated with subject's planned visits that are part of their standard-of-care, as long as the planned visits are within the protocol-specified visit windows. Either the investigator or a qualified subinvestigator will be required to see each subject at every study visit for clinical assessment of the subject's status.

An independent blinded Clinical Endpoint Committee (CEC) will apply the protocol definitions to adjudicate and classify efficacy and safety endpoint events. Throughout the double-blind treatment and 30-day post-treatment follow-up phases, suspected cases of DVT and PE will be centrally adjudicated by the CEC. In addition, incidental PE or DVT identified from routine care imaging (eg, CT scans ordered primarily for staging or restaging of malignancy) during the same time period will be adjudicated as asymptomatic PE or DVT events. Lastly, any clinical event that suggests the possibility that a major or clinically relevant non-major bleeding event occurred will be sent for adjudication. Emergent imaging results at the study site for clinical decision-making will be collected for the central adjudication by the CEC. In subjects who died during follow up, death certificates and if available, autopsy findings will be reviewed to establish a diagnosis of fatal PE.

If a subject permanently discontinues the study drug before the end of the double-blind treatment period (Day 180 visit), he/she should be instructed to complete an unscheduled EOT visit as soon as possible from the time that the study drug was discontinued, with the CU performed within 2 days of taking the last dose of study drug. A CU should not be performed at all if it is not possible to have it completed within 2 days of the last dose of study drug. In addition, the subject will be required to complete all remaining study visits and procedures, including what would have been their Day 180/EOT and Day 210/EOS visits. If the unscheduled EOT visit falls within the window of a remaining study visit, the subject does not need to repeat this required study visit.

The investigator should inform subjects of the importance of returning for all study visits (regardless of duration of study drug treatment) as it is imperative for the integrity of the study and results to have vital status and other outcomes ascertained. If the subject is unwilling or unable to return for any visits, or is lost-to-follow up, the investigator should collect as much follow-up information as possible for each remaining visit, including contacting the subject or legally acceptable representative by telephone or by mail to determine vital status and outcome ascertainment, as agreed to by the subject during the informed consent process. The site must document all attempts to try to contact the subject in the source documents.

An Executive Committee (EC) will be formed that has overall responsibility for the conduct and reporting of the study. The independent blinded CEC will apply the protocol definitions and adjudicate and classify any clinical event that suggests an efficacy or safety outcome event has occurred. The independent blinded CEC will also adjudicate all protocol-specified CU examinations. In addition, an unblinded Independent Data Monitoring Committee (IDMC) will periodically assess the safety of subjects in this study and evaluate the efficacy data as necessary to ensure that the safety of subjects is not compromised. All committees will be governed by independent charters.

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

SUBJECT POPULATION

The study will include ambulatory adult men and women, 18 years of age and older, with various cancer types with an expected survival of >6 months, who are scheduled to initiate systemic cancer therapy as a component of their standard-of-care anticancer regimen, have a baseline Khorana thromboembolic risk score of ≥2, and are judged by the investigator or qualified designee to be an appropriate candidate for treatment with either placebo or rivaroxaban for thromboprophylaxis based on their clinical status. The duration of the intended continued systemic cancer therapy will vary from subject to subject, and it is also understood that treatment modalities and drug combinations may change during the double-blind treatment period thereby reflecting current standards of clinical care.

DOSAGE AND ADMINISTRATION

Subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups: rivaroxaban 10 mg orally once daily or placebo 10 mg orally once daily for a maximum duration of treatment of 180 days (±3 days). Every effort should be made to initiate systemic cancer therapy on the same day as administration of the first dose of study drug, or within 72 hours of the first dose of study drug, when at all possible. However, for pragmatic reasons, subjects may be allowed to initiate systemic cancer therapy within a period of ±1 week prior to, or after their first dose of study drug, with a preference of this occurring within the first week following study drug administration, with the intention that systemic cancer therapy will continue during the double-blind treatment period for a duration determined by the treating oncologist according to standard protocols of clinical care. The initial dose of study drug should be taken on Day 1 at a time that is most convenient for the subject. Subsequent doses of study drug should be taken every 24±2 hours thereafter. The study drug can be taken with or without food and should be taken at the same time daily. In the event that a dose of study drug is missed, the missed dose should be taken as soon as possible. If a dose is missed, advise the subject to take the study drug as soon as possible on the same day and continue on the following day with their recommended daily dose regimen.

Interruption of study drug

The study drug may be temporarily interrupted; however, these interruptions should be kept to a minimum as much as possible. If a subject misses more than 14 consecutive days of study drug, he/she will need to permanently discontinue the study drug. It is recommended, when possible, that the study drug be discontinued at least 24 hours, and at the discretion of the investigator, before an invasive procedure (ie, surgical) to reduce the risk of bleeding. In deciding whether a procedure should be delayed at least 24 hours after the last dose of study drug, the increased risk of bleeding should be weighed against the urgency of intervention. In case of major surgery or major bleeding risk procedure, the investigator may consider holding the prior day's dose of study drug (skip both doses of the study drug the day before and the day of surgery), weighing the risk of bleeding against that of VTE. Consider bridging with parental anticoagulation, if

necessary. The study drug should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short. The investigator may consider resuming the study drug 24 hours after achieving hemostasis for low-bleeding risk or minor surgical procedures, and at 48 hours in case of major or high-risk bleeding procedures, noting that the time to onset of therapeutic effect is short.

During planned or emergency hospitalization, the study drug should be stopped only if the treating clinician determines that thromboprophylaxis or anticoagulation should be administered. It might be necessary to interrupt the study drug temporarily (eg, while the contraindicated mediation is taken). Subjects should resume the study drug as soon as it is deemed safe by the treating clinician, and study drug interruption during the treatment period should not exceed 14 consecutive days.

EFFICACY EVALUATIONS

Efficacy evaluations include assessment of subjects for VTEs that are part of the primary efficacy composite variable. The primary efficacy outcome variable is objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and VTE-related death. Key secondary efficacy outcomes are symptomatic VTE events (DVT/PE) and VTE-related deaths and all-cause mortality. Other secondary outcomes are individual components of the primary composite efficacy variable, confirmed fatal/non-fatal ATE events, confirmed fatal/non-fatal visceral VTE events, and composites of the primary endpoint. Any clinical event that suggests the possibility that an efficacy outcome event has occurred will be sent for adjudication.

The primary efficacy composite endpoint is the time from randomization to the first occurrence of objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, or VTE-related death occurring from randomization to the Day 180 visit as adjudicated by the independent blinded CEC. The key secondary efficacy endpoints include symptomatic VTE events (DVT/PE) and VTE-related deaths, and all-cause mortality from the time of randomization to the Day 180 visit. Other secondary efficacy endpoints include the time from randomization to the first occurrence for the following events during the 180-day, double-blind treatment period, defined as the individual components of the primary efficacy composite variable analyzed separately, confirmed fatal/non-fatal ATE events, and confirmed fatal/non-fatal visceral VTE events. In addition, a composite of symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and all-cause mortality, as well as a composite of symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, and VTE-related deaths will be assessed.

If a subject has a suspected efficacy outcome event during the study, the treating physician should exercise clinical judgment and follow guidelines to apply the standard-of-care.

Unblinding of the study drug should not be necessary, as anticoagulation regimens do not require adjustment, regardless of treatment group assigned when the study drug is administered in the doses used in this study.

SAFETY EVALUATIONS

Safety will be evaluated by the monitoring of bleeding events, AEs, clinical laboratory tests, pregnancy tests, Eastern Cooperative Oncology Group (ECOG) status, central venous catheter (CVC) status, concomitant therapies, and vital signs, including weight measurements. Additionally, the targeted medical history and physical examination performed at screening should be obtained and performed in a manner that facilitates the investigator's ability to make reasonable evidence-based clinical assessments and decisions throughout the study related to the safety evaluations or to the assessment of the efficacy evaluations.

The primary safety objective of this study is the time to a major bleeding event in treated subjects in each randomized treatment group as defined by ISTH. Bleeding events will be classified using protocol-specified definitions for major, clinically relevant non-major, or minor bleeding. Secondary safety endpoints include proportions of clinically relevant non-major bleeding, minor bleeding, and any bleeding (defined as major, clinically relevant non-major, and minor bleeding as defined by ISTH). Subjects will be censored for safety endpoints events up to 2 days after receiving the last dose of study drug.

Any clinical event that suggests the possibility that a major or clinically relevant non-major bleeding event occurred will be sent for adjudication. If a subject has a serious bleeding event during study drug treatment, routine measures should be considered. If these measures are sufficient to stop bleeding, unblinding of study drug should not be necessary.

BIOMARKER EVALUATIONS

Blood samples will be collected from subjects at screening, the Weeks 8 and 16 visits, and the Day 180/EOT visit to measure levels of circulating D-dimer, P-selectin, and Tissue Factor.

STATISTICAL METHODS

Statistical analysis for this clinical study data will be performed 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 (SAP).

Data collected on the primary efficacy, safety, as well as the key secondary endpoints will be summarized across treatment groups. Specific imputation rules for missing data (eg, missing event dates) will be applied, if warranted, and will be specified in the SAP before the final database lock. Descriptive statistics such as mean, median, standard deviation, interquartile range, minimum, and maximum will be used to summarize continuous variables. Counts and proportions will be used to summarize categorical variables. Graphical data displays (eg, box plots) may also be used to summarize data. Kaplan-Meier estimates adjusted for competing risk over time will be summarized and plotted for time-to-event variables.

Study Population/Analysis Sets

Following the intent-to-treat (ITT) principle, all randomized subjects will constitute the ITT population. The safety population is defined as a subset of the ITT population and consists of all randomized subjects who receive at least 1 dose of study drug. The per-protocol (PP) population is defined as a subset of the ITT population. Subjects with major protocol deviations will be excluded from the PP population. Major protocol deviations will be defined in the SAP. The primary efficacy and key secondary endpoint analyses in this study will be based on the ITT population. All safety endpoints will be analyzed based on the safety population.

Sample Size Determination

This is a 6-month fixed-duration study to demonstrate the superiority of rivaroxaban compared with placebo in ambulatory cancer subjects undergoing systemic cancer therapy. Estimates for VTE events in this population vary but in most studies, the data demonstrate a significant benefit (or, reduction in events) over placebo when cancer subjects are treated with anticoagulant therapy. According to a recent review of the VTE prophylaxis studies in cancer subjects by Khorana et al, the majority of RCTs in solid tumors have reported relative risk reductions (RRRs) between 50% and 64%. The duration of the earlier primary VTE prophylaxis studies in cancer was generally between 3 to 4 months, in conjunction with initiation of systemic anticancer therapy.

The basis for predictive events is derived from the Vienna Cancer and Thrombosis Study (CATS) group, which utilized the Khorana thromboembolic risk score, and followed 819 ambulatory cancer subjects for symptomatic VTE as an endpoint. In a Kaplan-Meier analysis, the cumulative probability of VTE after 6 months: Khorana thromboembolic risk score ≥3, 17.7% (95% confidence interval [CI]: 11.0% - 27.8%, N= 93), and 9.6% (95% CI: 6.2% - 14.7%, N=221) in those subjects with a Khorana thromboembolic risk score of 2. The addition of adjudicated objectively confirmed asymptomatic DVT and PE events is expected to contribute an additional 5% to 10% to the primary composite endpoint event rates.

Taken together, these results, along with a number of smaller epidemiologic studies, in general support a symptomatic VTE rate at 180 days of at least 9.5% in subjects with a Khorana thromboembolic risk score of ≥2 and therefore, an overall primary efficacy composite endpoint event rate of approximately 14.5% seems reasonable. Furthermore, it is assumed that the use of rivaroxaban will reduce this event rate to approximately 6.0%.

Assuming a cumulative incidence rate of 14.5% for the primary efficacy composite endpoint events in the placebo group and 6.0% cumulative incidence rate in the rivaroxaban treatment group, a total sample of about 700 randomized subjects (350 per treatment group) will be required to demonstrate approximately 60% RRR in the primary efficacy composite endpoint with a 2-sided Type 1 error rate of 5% and with >90% statistical power (calculation performed by EaST 6.3 software), assuming a 20% discontinuation rate. Towards the end of the enrollment phase, approximately 800 subjects were planned to be randomized into the study due to the high subject discontinuation rate.

Essentially, the above overall sample size estimate is calculated based on the following assumptions:

- Effect size: absolute difference in event rates = 8.5%, RRR = 58.6%
  - Primary efficacy composite endpoint event rate in the placebo arm: 14.5%
  - Primary efficacy composite endpoint event rate in the rivaroxaban arm: 6%
- Power: >90%
- Overall α level: 5%, 2-sided
- Probability of dropping out of the study: 20%
- Duration of enrollment period: 12 months
- Duration of study: 6 months (fixed for each randomized subject)

Interim Analysis

No interim efficacy analysis is planned in this study. An unblinded IDMC has been established for this study to periodically assess the safety of subjects in the study and evaluate the efficacy data, as necessary.

Efficacy and Safety Analyses

The primary efficacy and key secondary endpoint analyses in this study will be based on the ITT population. All safety endpoints will be analyzed based on the safety population. Statistical tests will be based on a 2-sided Type 1 error rate of 5%. Associated 95% CIs will be provided. Primary and secondary events will be adjudicated by an independent blinded CEC and analyses will be based on these adjudicated events. Investigator-reported events will also be summarized. Additional data analyses (including those based on specific subgroups) will be identified in the SAP.

Primary Efficacy Composite Endpoint Analysis

This analysis will be performed on a time-to-first-event basis during the observation period up to the Day 180 visit, using a stratified Cox proportional hazard model (stratification factor: APC or non-APC), including treatment group as a categorical explanatory variable with 2 levels (ie, rivaroxaban, placebo) and will be based on the ITT population. This primary efficacy analysis will include composite events (ie, objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE or VTE-related death) occurring from randomization up to the Day 180 visit for all randomly assigned subjects in the study. Subjects who have no primary efficacy outcome during this observation period, or subjects who are lost-to-follow up, or subjects who die because of other reasons than VTE, or subjects who withdraw informed consent before the end of the predefined treatment duration, will be censored at the last day of their complete assessment for study outcomes during the treatment period (assuming these types of censorings are independent of the primary outcome). Further details will be specified in the SAP.

To account for competing risks (deaths from causes other than VTE for efficacy, or fatal bleeding for safety) in the primary efficacy and safety analyses, a cumulative incidence approach will be followed with the use of Gray's 2-sample test (2-sided Type 1 error rate of 5%). Associated hazard ratios (HRs) and 95% CIs will be calculated with the use of the Fine and Gray regression model. Cumulative incidence functions will be estimated separately for the 2 randomized treatment groups. Additional statistical details regarding the specific models and inferential procedures to be used will be described in the SAP.

Key secondary efficacy endpoints will be analyzed in a similar fashion as the primary efficacy endpoint.

Safety Endpoints, Laboratory and Vital Signs Data Analysis

The primary safety endpoint includes time to a major bleeding event in treated subjects in each randomized treatment group as defined by ISTH. A statistical comparison of the 2 randomized treatment groups will be performed using a stratified Cox's proportional hazards model with treatment as a covariate. Additionally, the frequency of bleeding events in each treatment group will be summarized. Secondary safety endpoints, defined by proportions of clinically relevant non-major bleeding events, will also be summarized. All reported AEs (ie, treatment-emergent adverse events [TEAEs], AEs that have worsened since baseline) will be summarized.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe AE or serious adverse event (SAE). Laboratory data will be summarized and descriptive statistics for vital signs will be provided.

TIME AND EVENTS SCHEDULE

Period	Screening[a]	Double-Blind Treatment				Post-treatment (Follow up)
		Randomization[a]	Every 8-Week Visits (±7 days)		End of Treatment (EOT) Visit[b] (±3 days)	End of Study (EOS) Follow Up[c] (±7 days)
Month		-	2	4	6	7
Day/Week	Day -14 to -1	Day 1	Wk 8[o]	Wk 16[o]	Day 180[o]	Day 210
Eligibility						
Obtain informed consent	X					
Apply inclusion/exclusion criteria	X					
Demographics	X					
Relevant medical history	X					
Disease staging (using TNM system [solid tumors] or Ann Arbor [lymphoma])	X					
Perform physical examination (Record height/weight/BMI)	X					
Coagulation Tests (PT, aPTT and INR)	X					
Record prestudy drug(s)[d]	X	X				
Record Khorana thromboembolic risk score	X					
Randomization		X[e]				
Study Drug Administration						
Contact IWRS for study drug bottle number to dispense[e]		X	X	X		
Dispense study drug/provide instructions		X[f]	X	X		
Perform study drug accountability/compliance			X	X	X	
Safety Assessments						
Urine pregnancy test[g]	X				X	
Record vital signs including weight	X	X	X	X	X	
Record ECOG performance status[h]	X	X	X	X	X	
Record CVC status	X	X	X	X	X	
Collect laboratory samples (hematology, serum chemistry)[i]	X		X	X	X	
Calculated eGFR[j]	X		X	X	X	
Clinical events relevant to safety endpoints (bleeding events)[o]			X	X	X	X
Adverse events	X	X	X	X	X	X
Concomitant therapy[k]		X	X	X	X	X
Efficacy Assessments						
Perform CU	X		X	X	X[l]	
Clinical events relevant to efficacy endpoints (VTE)[o]			X	X	X	X
Telephone follow up for vital status						X
Exploratory Assessments						
Biomarker sample[m]	X		X	X	X	
PK sample			X[n]			

[a] Assess subject's continuing eligibility by reviewing any changes since screening based upon the scheduled assessments to be performed at this time. Screening and randomization may be performed on the same day if historical laboratory results (done per standard-of-care) are already available during the screening period (must have been previously drawn within 2 weeks of randomization), CU results are received from the local reader, and all required screening procedures are completed that qualify the subject. See footnote e.

[b] The Day 180/EOT visit will be performed at the completion of 180 ±3 days of treatment with study drug (regardless of whether a subject is ongoing in a cycle of systemic cancer therapy). If a subject permanently discontinues the study drug before the end of the double-blind treatment period (Day 180 visit), he/she should be instructed to complete an unscheduled EOT visit as soon as possible, from the time that the study drug was discontinued, and have the CU performed within 2 days of taking the last dose of study drug. At the unscheduled EOT visit, all procedures as outlined will be performed. In addition, subjects that permanently discontinue the study drug before the Day 180 visit will be required to complete all remaining study visits, including what would have been their Day 180/ EOT and Day 210/EOS visits.

[c] At the end of the post-treatment follow-up period (Day 210 visit), all subjects (or their legally acceptable representative), including those who discontinued the study drug prior to the Day 180 visit, will be contacted by telephone for an Day 210/EOS follow-up assessment.

[d] Prestudy therapies are those administered within 2 weeks before the first dose of study drug (Day 1). All prestudy therapies must be recorded in the eCRF except supplements such as fish oil, herbal medicines, and vitamins. The intent is to enroll subjects and begin the first dose of study drug before administration of systemic cancer therapy or radiotherapy, however, if for pragmatic reasons the subject begins systemic cancer therapy or radiotherapy prior to the first dose of study drug, the systemic cancer therapy or radiotherapy will be recorded in the appropriate section of the eCRF.

[e] An IWRS will be used to randomly assign subjects to treatment. Randomization may be completed once clinical laboratory results and imaging results (CU) from the local reader are available to confirm subject eligibility. Note: Historical laboratory results may be used for the screening visit to confirm eligibility; these results must be documented in the subjects' source documentation. In this case, subjects will be randomized on Day 1 based on the historical laboratory results, which must have been previously drawn within 2 weeks of randomization that confirms eligibility; however, screening blood samples must still be collected and sent to the central laboratory for analysis. Subsequently, if the screening results from the central laboratory indicate that the subject is not eligible, the historical laboratory results will take precedence and should be recorded in the eCRF to document eligibility.

[f] The initial dose of study drug should be taken on Day 1 at a time that is most convenient for the subject. Subjects will have up to 4 days to complete the Day 1 visit from the point of being randomly assigned to the study drug within IWRS (date of randomization) to initiate their study drug treatment in order to accommodate those subjects who will be receiving their study drug from a centralized drug depot; however, every effort should be made to initiate their study drug treatment within 1 day. Every effort should be made to initiate systemic cancer therapy on the same day as administration of the first dose of study drug, or within 72 hours of the first dose of study drug when at all possible. However, for pragmatic reasons, subjects may be allowed to initiate systemic cancer therapy within a period of ±1 week prior to or after their first dose of study drug. Subjects that are screened and initiate systemic cancer therapy more than 1 week before the first dose of study drug should not be randomized and will be considered a screen failure. However, if a subject does not initiate systemic cancer therapy as planned within +1 week after the first dose of study drug, the subject is allowed to continue taking study drug and remain in the study. Subsequent doses of study drug should be taken every 24±2 hours, thereafter. The study drug can be taken with or without food and should be taken at the same time daily. The maximum duration of study drug administration is 180 days ±3 days.

[g] To be performed on all women judged to be of childbearing potential. Additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy before administration of the study drug and throughout the study.

[h] The ECOG/WHO/Zubrod Performance Status Scale will be used to assess functional status (see Attachment 4).

[i] Hematology panel includes hemoglobin, hematocrit, RBC, WBC count with differential, and platelet count. Serum chemistry panel includes sodium, potassium, chloride, bicarbonate, BUN, glucose, uric acid, calcium, phosphate, albumin, total protein, creatinine, AST, ALT, total and direct bilirubin, and alkaline phosphatase.

[j] Estimated creatinine clearance will be calculated by the central laboratory using both the Modification of Diet in Renal Disease formula (see Attachment 5) as well as the Cockcroft-Gault formula (see Attachment 2). Either formula, as well as the CKD-EPI formula (see Attachment 6) can be used to determine eligibility at screening.

[k] All concomitant therapies taken throughout the double-blind treatment period for the treatment of AEs/SAEs, prohibited medications, additional medications as listed in Section 8 and systemic cancer therapy and radiotherapy must be recorded in the eCRF except supplements such as fish oil, herbal medicines, and vitamins. In addition, concomitant therapies should also be recorded beyond the Day 180/EOT visit only in conjunction with SAEs that meet the criteria outlined in Section 12.4.2. Serious Adverse Events.

[l] The Day 180/EOT visit will be completed within a window of ±3 days. The CU planned for the Day 180/EOT visit will be conducted preferably on the day of the visit or within the visit window (Day 180 ±3 days) but must be performed before the last dose of study drug. Subjects who discontinue early will have an unscheduled EOT visit as soon as possible from the time that the study drug was discontinued, with the CU performed within 2 days of taking the last dose of study drug. A CU should not be performed at all if it is not possible to have it completed within 2 days of the last dose of study drug.

[m] Blood samples will be collected for biomarker assessment (circulating D-dimer, P-selectin, and Tissue Factor).

[n] The blood sample for pharmacokinetic sample should be drawn prior to study drug administration at the Week 8 visit.

[o] Health care resource utilization data will be collected as part of the endpoint assessments, at Weeks 8 and 16, and Day 180/EOT, for all subjects, or until study drug discontinuation. The data collection will be specific to the study outcomes of DVT, PE, or bleeding, including visits to health care providers, hospitalization, length of hospitalization, and use of diagnostic procedures.

AE = adverse event; ALT=alanine aminotransferase; aPTT = activated partial thromboplastin time; AST=aspartate aminotransferase; BMI = body mass index; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CU = bilateral lower extremity venous duplex compression ultrasonography; CVC = central venous catheter; DVT = deep venous thrombosis; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EOS = end of study; EOT = end of treatment; INR = international normalized ratio; IWRS = Interactive Web Response System; PE = pulmonary embolism; PK=pharmacokinetic(s); PT = prothrombin time; RBC = red blood cell; SAE = serious adverse event; TNM = tumor, nodes, metastases; VTE = venous thromboembolism; WBC = white blood cell; WHO = World Health Organization; Wk = week.

ABBREVIATIONS

ACCP	American College of Chest Physicians
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
APC	advanced pancreatic cancer
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATE	arterial thromboembolism
BMI	body mass index
CEC	Clinical Endpoint Committee
CI	confidence interval
CrCl	creatinine clearance
CT	computed tomography
CU	bilateral lower extremity venous duplex compression ultrasonography
CVC	central venous catheter
CYP	cytochrome P450
DVT	deep vein thrombosis
EC	Executive Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EINSTEIN	oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis or pulmonary embolism
EOS	end of study
EOT	end of treatment
ESMO	European Society of Medical Oncology
FRAGEM	Gemcitabine with or without prophylactic weight-adjusted dalteparin in patients with advanced or metastatic pancreatic cancer: a multicenter, randomized Phase 3B trial
FXa	activated Factor X
GCP	Good Clinical Practice
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	intent to treat
IWRS	interactive web response system
LFT	liver function test
LMWHl	Low molecular weight heparin
MAGELLAN	The multicenter, randomized, parallel-group efficacy and safety study for the prevention of venous thromboembolism in hospitalized acutely ill medical patients comparing rivaroxaban with enoxaparin
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
PE	pulmonary embolism
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PQC	product quality complaint
PROSPECT-CONKO-004	A prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy trial
PROTECHT	Prophylaxis of thromboembolism during chemotherapy trial

PT	prothrombin time
RCT	randomized controlled trial
RECORD	REgulation of coagulation in ORthopedic surgery to prevent DVT and PE
RRR	relative risk reduction
SAE	serious adverse event
SAP	statistical analysis plan
SAVE-ONCO	Evaluation of AVE5026 in the prevention of VTE in cancer patients undergoing Chemotherapy
TEAE	treatment-emergent adverse event
ULMWH	ultra-low molecular weight heparin
ULN	upper limit of normal
VKA	vitamin K antagonist
VTE	venous thromboembolism
WHO	World Health Organization

1. INTRODUCTION

Rivaroxaban is a potent, orally administered and highly selective direct inhibitor of activated factor X (FXa); a protease enzyme that promotes blood coagulation by triggering an amplified burst of thrombin generation, ultimately leading to thrombus formation (a blood clot). Activated factor X plays a central role in the initiation and propagation of blood coagulation, being positioned at the intersection of the Contact Activation and Tissue Factor coagulation pathways formerly intrinsic and extrinsic, respectively. Therefore, selective inhibition of FXa by rivaroxaban is effective in reducing thrombin generation and clot formation.

Rivaroxaban is an oxazolidinone derivative. The S-configuration-oxazolidinone ring of rivaroxaban serves as the central core of the molecule and specifically directs morpholinone residue (essential for higher potency) into the S-4 pocket and the chlorothiophene moiety (essential for potent FXa inhibition) into the S-1 pocket of FXa.

As of 15 September 2014, more than 84,000 subjects have been enrolled in interventional clinical trials (completed and ongoing Phase 1, Phase 2, Phase 3, and Phase 4), including more than 47,000 subjects treated with rivaroxaban. Rivaroxaban has been approved for multiple thrombosis-mediated conditions worldwide under the trade name XARELTO®.[35] 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 (IB) for rivaroxaban.[6] 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

Nonclinical Studies

Comprehensive toxicologic investigations of rivaroxaban have been performed. No clinicopathologic or histopathologic evidence of hepatotoxicity has been observed in any of the animal species tested (mice, rats, and dogs). Preclinical pharmacology studies of rivaroxaban[31] showed:

- Competitive, selective, direct inhibition of human FXa
- Inhibition of prothrombinase with resultant anticoagulant activity but no significant interaction with platelet function
- Species-dependent inhibition of FXa with resultant antithrombotic activity in venous and arterial thrombosis models in rats and rabbits
- A high degree of correlation between clotting times (eg, prothrombin time [PT]) and plasma drug levels
- Antithrombotic activity without excessive prolongation of bleeding time in rats and rabbits
- Bleeding risk comparable with enoxaparin
- Co-administration of rivaroxaban with acetylsalicylic acid (aspirin), naproxen, diclofenac, clopidogrel, or warfarin showed additive but not potentiating effects on bleeding time prolongation in the tail transection model in rats.

Toxicologic data indicated no need for follow up in the clinical studies.

Clinical Studies

As of 15 September 2014, more than 84,000 subjects have participated in completed Phase 1, 2, 3, and 4 studies of rivaroxaban. The Phase 1 program for rivaroxaban included 70 studies with a total 1,610 subjects who received rivaroxaban as active treatment. The clinical indication program has completed 30 studies; 12 Phase 2 studies, 17 Phase 3 studies, and 1 Phase 4 study with in total approximately 49,023 subjects receiving rivaroxaban, 32,293 subjects receiving active comparator, and 6,868 subjects receiving placebo treatments. The efficacy and safety of rivaroxaban has been studied in several large clinical development programs for the prevention and treatment of multiple thrombosis-mediated conditions.

Rivaroxaban has been demonstrated to be highly effective in a number of clinical settings, including venous thromboembolism (VTE) prophylaxis in the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE) (RECORD) 1-3 studies in 9,500 subjects undergoing hip and knee replacement surgery,[13,18,23] and in the secondary prevention of VTE in the Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients with Acute Symptomatic Deep Vein Thrombosis or Pulmonary Embolism (EINSTEIN) trials in 8,900 subjects with an acceptable benefit-risk profile.[40,41]

Clinical experience with rivaroxaban in primary and secondary VTE prophylaxis in active cancer subjects

Small subgroups of subjects with active cancer received prophylaxis/treatment with rivaroxaban in The Multicenter, Randomized, Parallel-group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin (MAGELLAN) and EINSTEIN studies.[32] In the MAGELLAN study, 8,101 subjects at least 40 years of age or older who were hospitalized for an acute medical illness were randomly assigned to receive VTE prophylaxis with subcutaneous enoxaparin, 40 mg once daily, for 10±4 days and oral placebo for 35±4 days or to receive subcutaneous placebo for 10±4 days and oral rivaroxaban, 10 mg once daily, for 35±4 days.[11]

The MAGELLAN study was a prospective, randomized, double-blind, double-dummy, active comparator-controlled, multicenter and multinational study. Acutely ill subjects (admitted to the hospital no more than 72 hours prior to randomization) who did not require surgery, were completely immobilized for at least 1 day during the hospitalization, were anticipated to have a decreased level of mobility for at least 4 days, and met all other inclusion criteria were eligible for randomization to receive subcutaneous enoxaparin 40 mg once daily for 10±4 days and oral placebo for 35±4 days or to receive subcutaneous placebo for 10±4 days and oral rivaroxaban 10 mg once daily for 35±4 days. MAGELLAN enrolled a general medically ill subject population, selected based on set criteria for risk factors such as age, immobility, cancer, and type of index event but unselected from a validated VTE risk score perspective. This population included a high proportion of subjects who were ≥75 years of age (38.3%) or had heart failure (38.6 %) at baseline, and were hospitalized for an acute episode of infection (45%)

or heart failure (32.3%). The primary objectives of this study were to demonstrate superior efficacy at Day 35 in the modified intent-to-treat (ITT) population (Primary Efficacy Endpoint 1) and noninferiority at Day 10 in the per-protocol (PP) population.[11] The primary endpoint was a composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic non-fatal PE and VTE-related death.

A total of 592 subjects (7.3%) had active cancer at baseline. Although the subset of cancer subjects was too small to merit a meaningful analysis, there were numerical differences (as measured by the relative risk) between the 2 treatment arms that favored enoxaparin with respect to primary efficacy, major bleedings, and clinically relevant bleedings. The primary efficacy endpoint showed subjects treated with rivaroxaban 20/202 (9.9%) and enoxaparin 15/203 (7.4%) relative risk: 1.340; 95% confidence interval [CI]: 0.706 to 2.542. Major bleeding occurred in subjects treated with rivaroxaban 7/294 (2.4%) and enoxaparin 0 (data on file).

Subjects with active cancer were also treated with rivaroxaban for secondary prophylaxis of recurrent VTE in the EINSTEIN clinical program. In a pooled subgroup analysis, from the EINSTEIN-DVT and EINSTEIN-PE trials (2 randomized, open-label, Phase 3 studies) that compared rivaroxaban with enoxaparin given with and followed by a Vitamin K antagonist (VKA) for the treatment of DVT (EINSTEIN-DVT) or PE (EINSTEIN-PE),655 (8%) subjects were diagnosed with any active cancer, 462 (6%) presented with the diagnosis at baseline, and 193 (2%) were diagnosed with cancer during the study.[40,41]

In subjects with active cancer (diagnosed at baseline or during treatment), recurrent VTE occurred in 16 (5%) of 354 subjects allocated to rivaroxaban and 20 (7%) of 301 subjects allocated to enoxaparin and VKA (hazard ratio [HR] 0.67, 95% CI 0.35 to 1.30). Clinically relevant bleeding occurred in 48 (14%) of 353 subjects receiving rivaroxaban and in 49 (16%) of 298 subjects receiving low molecular weight heparin (LMWH)/VKA therapy (HR 0.80, 95% CI: 0.54 to 1.20). Major bleeding occurred in 8 (2%) of 353 subjects receiving rivaroxaban and in 15 (5%) of 298 subjects receiving combination therapy (HR 0.42, 95% CI: 0.18 to 0.99).

1.2. Overall Rationale for the Study

Patients with cancer are at 4 to 7 times higher risk of VTE than patients without cancer.[8,17] The risk for VTE varies according to several factors, including age, obesity, history of thrombosis, and recent reduced mobility.[15] In addition, the VTE risk associated with cancer varies throughout the course of the disease. The risk is particularly high in the first few months following diagnosis and there is an estimated 4-fold to 13-fold increase in risk for VTE in late-stage metastatic disease.[8, 9, 10] Cancer treatment also has an important impact on the development of VTE, with systemic cancer therapy increasing the VTE risk by up to 6.5-fold.[9, 17]

In patients with cancer, VTE is associated with substantial morbidity and complicates the clinical management of cancer. Emerging research indicates a detrimental effect of VTE on cancer survival.[2, 3, 4, 10] Venous thromboembolism is currently recognized as the second leading cause of death in patients with cancer.[21] The incidence of cancer-associated thrombosis has increased,[20,21,29,38] probably because of a combination of factors including improved treatment

outcomes resulting in longer patient survival, more aggressive and prothrombotic treatment regimens, an aging population, and increased detection owing to improvements in imaging technology and the increased frequency of imaging.

A recent real-world retrospective analysis involving 27,479 patients in a health care claims database, suggests that the actual rate of VTE may be higher than that reported in clinical trials.[24] This analysis assessed the rate of VTE at 3.5 months after the initiation of systemic cancer therapy and again at 12 months. In this study, the rate of reported VTE at 3.5 months after the initiation of systemic cancer therapy was 7.3% (range, 4.6% to 11.6%), and the cumulative risk continued to increase over time to a rate of 13.5% (range, 9.8% to 21.3%) at 12 months. The highest VTE risk was observed in those patients receiving systemic cancer therapy for tumors of the pancreas, stomach, and lung.[9, 10, 21]

Current guidelines from the American College of Chest Physicians (ACCP),[19] the American Society of Clinical Oncology (ASCO),[25] the European Society of Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN)[39] have subtle differences, but none recommend the routine use of VTE prophylaxis in most ambulatory patients with cancer due to limited randomized controlled trial (RCT) data and uncertainty on the benefit/risk in the ambulatory cancer population. An exception is made for patients with multiple myeloma who require treatment with thalidomide or lenalidomide in combination with systemic cancer therapy or high-dose dexamethasone; among these patients, rates of VTE of 23% to 75% have been reported.[14]

The low overall risk of studied populations in RCTs (ie, in unselected subjects with low VTE risk requiring high numbers needed to treat), high cost for injectables in the United States, and logistical issues related to daily patient self-injections have been considered in the current guideline recommendations.

Two prospective studies, Gemcitabine with or without Prophylactic Weight-adjusted Dalteparin in Patients with Advanced or Metastatic Pancreatic Cancer: A Multicentre, Randomized Phase 3b trial (FRAGEM) and A Prospective, Randomized Trial of Simultaneous Pancreatic Cancer Treatment with Enoxaparin and Chemotherapy (PROSPECT-CONKO-004) trial, evaluated the clinical benefit of the administration of LMWH plus gemcitabine-based systemic cancer therapy in advanced pancreatic cancer (APC) subjects.[27,34] The FRAGEM trial was a Phase 2b RCT of 123 patients. Venous thromboembolism was reduced from 28% to 12%, with a relative risk of 0.42 (95% CI: 0.19 to 0.94; p =.039). No differences in rates of major bleeding or mortality between study arms were observed. In the PROSPECT-CONKO-004 study, enoxaparin decreased the rate of symptomatic VTE after 3 months (control 9.87%; enoxaparin 1.25%) and 12 months (control 15%; enoxaparin, 5%).

The largest studies of prophylaxis of VTE, the Prophylaxis of Thromboembolism during Chemotherapy Trial (PROTECHT)[1] and the Evaluation of AVE5026 in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy (SAVE-ONCO study),[2] showed decreased rates of events among subjects who were receiving systemic cancer therapy. In these clinical trials, the overall rates of VTE among subjects who

were receiving placebo were low, ranging from 3% to 4%. The rates of minor bleeding in the PROTECHT and SAVE-ONCO studies were similar among the subjects receiving prophylactic anticoagulant therapy and those receiving placebo. The PROTECHT study was not powered to detect differences in major bleeding. In the SAVE-ONCO study, no increase in major bleeding was observed in subjects receiving prophylactic treatment as compared with placebo.

Although RCTs of LMWH or ultra-low molecular weight heparin (ULMWH) prophylaxis have shown that anticoagulation therapy in ambulatory subjects with cancer is associated with a significant reduction in the relative risk of VTE, the difference in absolute risk was small, necessitating a large number of subjects to receive prophylaxis to save one event (eg, number needed to treat = 45 in SAVE-ONCO). Suggested reasons for the low VTE rates in these studies, as compared with those in real-world observational studies, include possible selection of lower-risk subjects combined with relatively short follow-up treatment periods. In addition the VTE risk associated with cancer varies throughout the course of the disease. This risk is particularly high after the start of the anticancer treatment, during the first months after cancer diagnosis, and at the end-stage of disease and may not be fully assessed during a 3-month period of observation.

Early detection of asymptomatic PE through computed tomography (CT) imaging procedures while restaging after systemic cancer therapy, and treatment of those events with full-dose anticoagulation have become routine. Two studies comparing rates of recurrent VTE, bleeding, and death between cancer subjects who received anticoagulation for incidentally detected PE and those who received anticoagulation therapy for symptomatic PE showed no significant difference in outcome between the 2 groups. Both studies confirm that subjects with incidentally detected PE benefit from anticoagulation as much as subjects with symptomatic PE.[12,24]

In summary, VTE results in increased morbidity, mortality, and complexity of care in subjects with cancer, and may also lead to delays in surgery and the administration of systemic cancer therapy as well as an increased risk of bleeding associated with therapeutic anticoagulation. Routine thromboprophylaxis is currently not recommended by treatment guidelines, given the lack of substantial proven benefit in this population.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objectives

The primary efficacy objective is to demonstrate that rivaroxaban is superior to placebo for reducing the risk of the primary composite outcome as defined by objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and VTE-related death in ambulatory adult subjects with various cancer types receiving systemic cancer therapy who are at high risk of developing a VTE.

Secondary Objectives

The key secondary efficacy objectives of this study are to compare the efficacy of rivaroxaban with placebo for reducing the risk of symptomatic VTE events and VTE-related deaths, and all-cause mortality in ambulatory adult subjects with various cancer types receiving systemic cancer therapy who are at high risk of developing a VTE. Other secondary efficacy objectives include the evaluation of the individual components of the primary efficacy composite variable, confirmed fatal/non-fatal arterial thromboembolism (ATE) events, confirmed fatal/non-fatal visceral VTE events, a composite of symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and all-cause mortality, and a composite of symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, and VTE-related deaths.

Safety Objectives

The primary safety objective of this study is to assess the major bleeding events (as defined by the International Society on Thrombosis and Hemostasis [ISTH]).[37] In addition, clinically relevant non-major bleeding, minor bleeding, and any bleeding (defined as major, clinically relevant non-major, and minor bleeding) will be assessed as measured by the ISTH definition.

Exploratory Objectives

The exploratory objectives of this study are:

- To assess inflammation- and hypercoagulability-related biomarkers including D-dimer, P-selectin, and Tissue Factor
- To analyze the steady state pharmacokinetics (PK) and exposure response of rivaroxaban
- To collect health care resource utilization (HCRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this study)

2.2. Hypothesis

The primary hypothesis of this study is that prophylactic treatment with rivaroxaban administered at a dose of 10 mg once daily for up to 6 months will be superior to placebo in reducing the risk of objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and VTE-related death in ambulatory adult subjects with various cancer types receiving systemic cancer therapy who are at high risk of developing a VTE.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, superiority study comparing the efficacy and safety of rivaroxaban with placebo for primary prophylaxis of

VTE (defined as DVT and/or PE) in ambulatory adult men and women, 18 years of age and older, with various cancer types who are scheduled to initiate systemic cancer therapy as a component of their standard-of-care anticancer regimen, who have a baseline Khorana thromboembolic risk score of ≥2, and are judged by the investigator or qualified designee to be an appropriate candidate for treatment with either placebo or rivaroxaban for thromboprophylaxis based on their clinical status. The duration of the intended continued systemic cancer therapy will vary from subject to subject, and it is also understood that treatment modalities and drug combinations may change during the double-blind treatment period thereby reflecting current standards of clinical care.

Initially, a target of approximately 700 subjects were to be randomly assigned into the study in a 1:1 ratio to 1 of 2 treatment groups with approximately 350 subjects per treatment group, with an assumed rate of discontinuation of approximately 20% from the study as described in Section 6, Dosage and Administration. Towards the end of the enrollment phase, approximately 800 subjects were planned to be randomized into the study due to the high subject discontinuation rate. In addition, subjects will be stratified at randomization by tumor type (APC or non-APC); it is estimated that approximately 25% of the subjects randomly assigned are those with APC.

The study consists of 3 periods: a 2-week screening period, a 180-day double-blind treatment period with an end-of-treatment (EOT) visit, and a 30-day post-treatment follow-up period with a Day 210/end-of-study (EOS) visit. The duration of participation in the study for each subject is approximately 32 weeks.

At the screening visit (Day -14 to -1), designated study personnel will explain the nature of the study, including all relevant details, and obtain written informed consent from the subject before initiation of any study-related procedures. Once all required screening procedures are completed, qualifying laboratory results are received, and bilateral lower extremity venous duplex compression ultrasonography (CU) results are received from the local reader, subjects will be asked to return to the study site as soon as possible, but no more than 14 days after the screening visit, for the randomization (Day 1) visit. Subjects found to have baseline DVT on screening CU or incidental DVT or PE as identified from routine care imaging (eg, spiral CT scans ordered primarily for staging or restaging of malignancy) within 30 days prior to randomization will not be eligible for randomization. Subjects may be rescreened once, if not randomized after the initial screening. All screening procedures must be repeated if rescreening is performed after the initial 2-week screening period.

During the double-blind treatment phase, from the time of randomization to the last dose of study drug at the Day 180 visit, imaging of suspected cases of DVT and non-fatal PE will be adjudicated. In addition, incidental PE or DVT identified from routine care imaging (eg, CT scans ordered primarily for staging or restaging of malignancy) during the same time period will be adjudicated as asymptomatic PE or DVT events as well.

Eligible subjects will be randomly assigned by an Interactive Web Response System (IWRS), in a 1:1 ratio to receive 1 of 2 treatments during the double-blind treatment period: rivaroxaban 10 mg orally once daily or placebo 10 mg orally once daily for a maximum of

180 days (±3 days). Subjects will be stratified at randomization by tumor type (APC or non-APC) and will be instructed to take the study drug for a fixed duration of 180 days (±3 days). Subjects will have up to 4 days to complete the Day 1 visit from the point of being randomly assigned to the study drug within IWRS (date of randomization) to initiate their study drug treatment in order to accommodate those subjects who will be receiving their study drug from a centralized drug depot; however, every effort should be made to initiate study drug within 1 day. Every effort should be made to initiate systemic cancer therapy on the same day as administration of the first dose of study drug, or within 72 hours of the first dose of study drug when at all possible. However, for pragmatic reasons, subjects may be allowed to initiate systemic cancer therapy within a period of ±1 week prior to, or after their first dose of study drug, with a preference of this occurring within the first week following study drug administration.

Subjects will have study visits, inclusive of visit windows, performed at Week 8 (±7 days), Week 16 (±7 days), and Day 180/EOT (±3 days) during the double-blind treatment period, and will undergo mandatory CU at these visits. The CU planned for the Day 180/EOT visit must occur within the specified ±3-day window and before the last dose of study drug. Following a 30-day post-treatment follow-up period (Day 210 ±7 days from randomization), all subjects (or their legally acceptable representative), including those who discontinued the study drug prior to the Day 180 visit, will be contacted by telephone for a Day 210/EOS visit follow-up assessment and will have their vital status (eg, dead, alive, or lost-to-follow up) as well as clinical status review for suspected outcome and safety bleeding events completed. Adverse events (AEs) will be collected as specified in Section 12, Adverse Event Reporting and concomitant medications will be collected as specified in Section 8, Prestudy and Concomitant Therapy.

All study visits may be coordinated with subject's planned visits that are part of their standard-of-care, as long as the planned visits are within the protocol-specified visit windows. Either the investigator or a qualified subinvestigator will be required to see each subject at every study visit for clinical assessment of the subject's status.

An independent blinded Clinical Endpoint Committee (CEC) will apply the protocol definitions to adjudicate and classify efficacy and safety endpoint events. Throughout the double-blind treatment and 30-day post-treatment follow-up phases, suspected cases of DVT and PE will be centrally adjudicated by the CEC. In addition, incidental PE or DVT identified from routine care imaging (eg, CT scans ordered primarily for staging or restaging of malignancy) during the same time period will be adjudicated as asymptomatic PE or DVT events. Lastly, any clinical event that suggests the possibility that a major or clinically relevant non-major bleeding event occurred will be sent for adjudication. Emergent imaging results at the study site for clinical decision-making will be collected for the central adjudication by the CEC. In subjects who died during follow up, death certificates and if available, autopsy findings will be reviewed to establish a diagnosis of fatal PE.

If a subject permanently discontinues the study drug before the end of the double-blind treatment period (Day 180 visit), he/she should be instructed to complete an unscheduled EOT visit as soon

as possible from the time that the study drug was discontinued, with the CU performed within 2 days of taking the last dose of study drug. A CU should not be performed at all if it is not possible to have it completed within 2 days of the last dose of study drug. In addition, the subject will be required to complete all remaining study visits and procedures, including what would have been their Day 180/EOT and Day 210/EOS visits (see TIME AND EVENTS SCHEDULE). If the unscheduled EOT visit falls within the window of a remaining study visit, the subject does not need to repeat this required study visit.

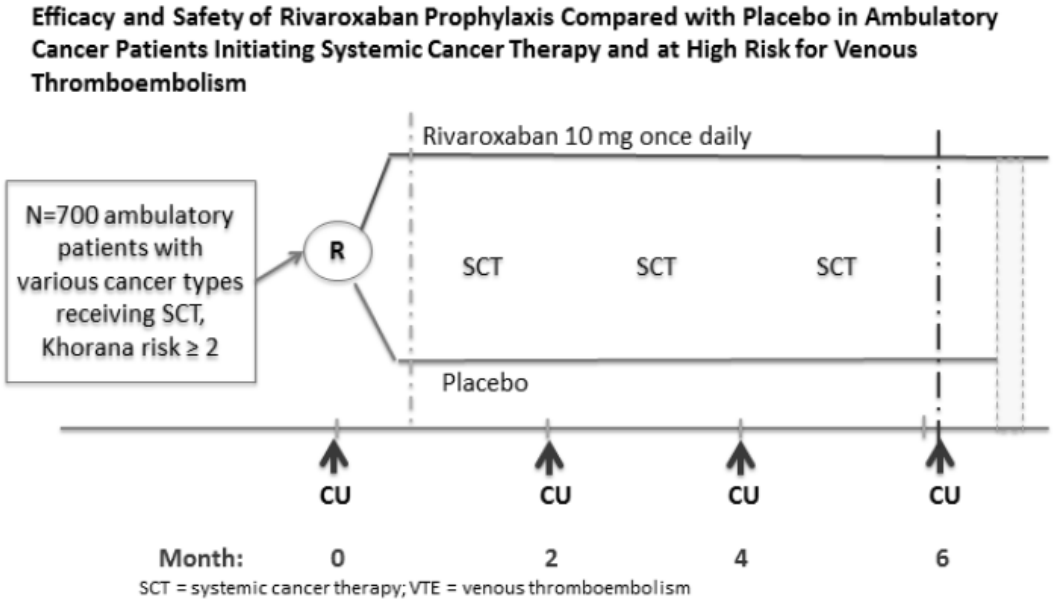
The investigator should inform subjects of the importance of returning for all study visits (regardless of duration of study drug treatment) as it is imperative for the integrity of the study and results to have vital status and other outcomes ascertained. If the subject is unwilling or unable to return for any visits, or is lost-to-follow up, the investigator should collect as much follow-up information as possible for each remaining visit, including contacting the subject or legally acceptable representative by telephone or by mail to determine vital status and outcome ascertainment, as agreed to by the subject during the informed consent process. The site must document all attempts to try to contact the subject in the source documents.

An Executive Committee (EC) will be formed that has overall responsibility for the conduct and reporting of the study. The independent blinded CEC will apply the protocol definitions and adjudicate and classify any clinical event that suggests an efficacy or safety outcome event has occurred. The independent blinded CEC will also adjudicate all protocol-specified CU examinations. In addition, an unblinded Independent Data Monitoring Committee (IDMC) will periodically assess the safety of subjects in this study and evaluate the efficacy data as necessary to ensure that the safety of subjects is not compromised. All committees will be governed by independent charters.

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

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

Figure 1: Schematic Overview of the Study



3.2. Study Design Rationale

Choice of Study Population

For the current study, ambulatory men and women, 18 years of age and older with various cancer types with an expected survival of >6 months, who are scheduled to initiate systemic cancer therapy as a component of their standard-of-care anticancer regimen, have a baseline Khorana thromboembolic risk score of ≥2, and in the judgment of the investigator or qualified designee are appropriate candidates for being randomized to either placebo or rivaroxaban for thromboprophylaxis based on clinical status will be enrolled.

The 2013 ASCO VTE Guidelines Panel recommends against the use of single risk factors or biomarkers to identify patients at high risk for VTE.[24] The Panel recommends the use of a risk score that incorporates multiple variables to identify high-risk patients. A risk assessment score for VTE, known as the Khorana thromboembolic risk score, was validated in cancer patients treated with chemotherapy and was recently updated to include renal tumors in the high-risk category. According to this risk model, 2 points were assigned for a thromboembolic "very high-risk" site of cancer (stomach, pancreas, or brain*) and 1 point for a "high-risk" site of cancer (lung, lymphoma, gynecologic, bladder, renal, or testicular).[22] In addition, 1 point each was added for a platelet count of 350 x 10^9/L or more, hemoglobin less than 10 g/dL and/or use of erythropoiesis-stimulating agents, leukocyte count more than 11 x 10^9/L, and body mass index (BMI) of 35 kg/m^2 or more. A Khorana thromboembolic risk score of ≥2 is required for inclusion into this study. (*Note: subjects with brain tumors are excluded from participation in this study).

Randomization and Blinding

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

Rationale for Treatment and Dose Selection

Rivaroxaban

Current ASCO, ESMO, and NCCN guidelines do not recommend the routine use of VTE prophylaxis in most ambulatory patients with cancer due to the paucity of randomized clinical study data,[25,28,39] and no agent is currently approved for this indication. Therefore, there is clinical equipoise and the proposed study is designed as a randomized, placebo-controlled study.

There is substantial supportive evidence that treatment with rivaroxaban 10 mg daily will be effective in the prevention of VTE in cancer patients. The selection of the rivaroxaban dose is based primarily on the results of the studies (involving 3,283 subjects) conducted for the prophylaxis of VTE in subjects undergoing knee or hip replacement surgery, where 10 mg daily of rivaroxaban resulted in a 2.6% to 9.2% reduction in VTE with an acceptable risk profile.[13,18,23] Data from the subgroup of subjects with cancer in the MAGELLAN and EINSTEIN studies provides some experience with rivaroxaban 10 to20 mg in subjects with cancer, but these studies were not specifically designed to evaluate thromboprophylaxis with rivaroxaban in a high-risk cohort of subjects with cancer undergoing chemotherapy. The current population with cancer is expected to have a lower mean age and fewer comorbidities compared with the hospitalized medically ill subjects enrolled in the MAGELLAN study. Clinically relevant bleeding in the subjects with cancer in the pooled analysis of the EINSTEIN studies treated with rivaroxaban 15 to 20 mg were similar to the rates in the enoxaparin/VKA antagonist groups and there were significantly fewer major bleeding events in the rivaroxaban treatment group with cancer. Numerically fewer major bleeding events were also observed when the rivaroxaban group was further sub-divided by age, body weight, and creatinine clearance (CrCl).[32]

Rationale for Duration of Therapy

The duration of the earlier primary prophylaxis studies was generally between 3 to 4 months, in conjunction with initiation of systemic anticancer therapy. However a more recent real-world retrospective analysis involving 27,479 patients in a health care claims database, suggests that the actual risk of VTEs continues to increase over time from 7.3% (range, 4.6% to 11.6%) at 3.5 months, to a cumulative risk of 13.5% (range, 9.8% to 21.3%) at 12 months.[24] Therefore, given the compounding nature of VTE risk in cancer patients on chemotherapy, a 3-month period of observation may prove insufficient to properly evaluate the benefit/risk of thromboprophylaxis. The proposed study will broaden the window of observation to 6 months following initiation of a new regimen of systemic cancer therapy, allowing for better categorization of the benefit/risk of thromboprophylaxis in this population.

The projected duration of 180 days of subject exposure to study drug was selected to ensure sufficient primary VTE prevention coverage for cancer subjects who typically undergo several cycles of systemic cancer therapy. Thus, the duration of the double-blind treatment period for this study was selected to be long enough to more rigorously evaluate the extent to which rivaroxaban can safely prevent VTE events in this selected study population. This approach will ensure that an adequate number of events will be accrued in order to perform a robust, well-powered primary analysis and draw definitive conclusions relating to the primary hypothesis.

Rationale for Mandatory Bilateral Lower Extremity Venous Compression Ultrasonography

The frequency of VTE in cancer subjects is likely to be substantially underestimated as the rates of clinical diagnosis are low compared with rates observed at autopsy.[5,16,30] Many factors limit the proper diagnosis of VTE in the ambulatory setting. There may be minimal or no symptoms or symptoms may be wrongly attributed to issues related to active cancer, eg, shortness of breath to lung metastases, or lower extremity edema to pelvic adenopathy. Many cases of PE present without symptoms of DVT, and many clinicians' index of suspicion for VTE is low in ambulatory subjects.

An important feature of this study is the use of screening to detect asymptomatic VTE. Although symptomatic disease is most important, many cases of DVT and PE are asymptomatic. Asymptomatic DVT identified by screening represents a subclinical manifestation of disease, and recommendations for prophylaxis are largely based on studies that used such routine screening approaches. Both European regulatory agencies and the United States Food and Drug Administration accept this approach in evaluating registration studies. Staging and restaging scans conducted in subjects with cancer may identify asymptomatic or incidental PE as well, and recent data suggest that such incidentally discovered PE is clinically relevant.

Compression ultrasonography is regarded as the standard method for the diagnosis of symptomatic, proximal vein thrombosis because of its low level of invasiveness and high sensitivity.[26,33] For example, using this approach in non-ambulatory cancer patients without DVT symptoms, the rate of asymptomatic DVT was 34% (comprised of asymptomatic proximal DVT in 11% and asymptomatic distal DVT in 23% of patients).[7] Although rates of isolated distal lower extremity DVT are typically much higher than proximal DVT events detected using CU, isolated distal DVT events will not be included in the primary efficacy outcome mainly due to controversy about its overall clinical significance.[42] A prospective cohort study in subjects after total hip or knee arthroplasty showed that CU has a positive predictive value of 71% compared with 25% for clinical examination, as well as an 83% and 11% sensitivity, respectively.[36] The Joint American Academy of Family Physicians/American College of Physicians Panel on DVT/PE recommend use of CU for patients with at least an intermediate pretest probability of lower extremity DVT.[42]

Choice of Efficacy Outcome/Endpoint

The primary efficacy outcome variable is the composite of any symptomatic/asymptomatic DVT, symptomatic non-fatal PE, incidental PE, and VTE-related death.

In this study, the primary efficacy composite endpoint is the time from randomization to the first occurrence of objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, or VTE-related death occurring from randomization to the Day 180 visit as adjudicated by the independent blinded CEC.

Evolution in cancer patient clinical management has resulted in increased frequency of medical imaging as part of staging protocols. In fact, incidental thromboembolism is often detected during diagnostic imaging, and it has been shown to be clearly associated with higher cancer mortality. In a study that analyzed a total of 1,151 radiologic exams of 135 APC subjects, incidental events comprised 33.3% of PEs, 21.4% of DVTs and 100% of visceral VTE. In these subjects, DVT (HR 25, 95% CI: 10 - 63, p <0.0001), PE (HR 8.9, 95% CI: 2.5 - 31.7, p = 0.007), and incidental visceral events (HR 2.6, 95% CI: 1.6 - 4.2, p = 0.0001) were all independently associated with mortality. There was no significant difference between asymptomatic and symptomatic events in terms of conditional survival at 3 or 6 months post diagnosis.

Choice of Safety Measures

The primary safety endpoint of this study is the time to a major bleeding event in treated subjects in each randomized treatment group as defined by ISTH.[37] Bleeding events will be classified using protocol-specified definitions for major, clinically relevant non-major, or minor bleeding. Secondary safety endpoints include the proportion of clinically relevant non-major bleeding, minor bleeding, and any bleeding (defined as major, clinically relevant non-major, and minor bleeding as defined by ISTH; for details on definitions, see Section 9.3, Safety Evaluations). Subjects will be censored for safety endpoints events up to 2 days after receiving the last dose of study drug.

As rivaroxaban has been or is being tested against an active comparator or placebo in studies that include over 89,000 subject-participants in the Phase 2/3/4 clinical studies of the rivaroxaban clinical development program, the AE profile of rivaroxaban has been well described and experience relative to the safe conduct of clinical studies is extensive. For example, over 12,000 subjects participated in the published Phase 3 RECORD studies of primary VTE prevention in subjects undergoing elective total hip/knee replacement alone. Additional characterization of the AE profile of rivaroxaban was reported using data from the EINSTEIN-DVT, EINSTEIN-PE, EINSTEIN-Extension, ROCKET-AF, ATLAS 2, and MAGELLAN Phase 3 clinical studies.

Subjects will have safety assessments conducted at each study visit, including the monitoring of bleeding events, AEs, clinical laboratory tests, pregnancy tests, Eastern Cooperative Oncology Group (ECOG) status, central venous catheter (CVC) status, concomitant therapies, and vital signs, including weight measurements. Hematology panel includes hemoglobin, hematocrit, red

blood cell count (RBC), white blood cell (WBC) count with differential, and platelet count. Screening serum chemistry panel includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), glucose, uric acid, calcium, phosphate, albumin, total protein, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin, and alkaline phosphatase.

Biomarker Collection

Biomarker samples will be collected to evaluate objectively measured indicators of pathologic and biologic processes associated with inflammation and hypercoagulability in blood, at baseline, Week 8, Week 16, and Day 180/EOT.

Medical Resource Utilization

Health care resource utilization (HCRU) data will be collected as part of the endpoint assessments at Weeks 8 and 16, and Day 180/EOT for all subjects and compared between the treatment groups, or until study drug discontinuation.

4. SUBJECT POPULATION

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 must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

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

4.1. Inclusion Criteria

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

1. Criterion modified per Amendment-3

   1.1 Ambulatory men and women, ≥18 years of age;

2. Have histologically confirmed solid malignancy including but not limited to: pancreas, lung, stomach, colon, rectum, bladder, breast, ovary, renal, or lymphoma (hematologic), with locally advanced or metastatic disease;

3. Have an ECOG Performance Status of 0-2 (see Attachment 4, Functional Status Assessment Tool);

4. Have a Khorana thromboembolic risk Score ≥2 (see Attachment 3, Cancer-Associated Venous Thromboembolism Risk Score);

5. Criterion modified per Amendment-3

   5.1. Have adequate renal function: CrCl ≥30 mL/min, (calculated using the Cockcroft-Gault formula [Attachment 2], the Modification of Diet in Renal Disease formula [Attachment 5], or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating GFR [Attachment 6]).

6. Criterion modified per Amendment-3

   6.1. Plan to initiate systemic cancer therapy within ±1 week of receiving the first dose of study drug with the intention of receiving systemic cancer therapy during the double-blind treatment period for an intended duration determined by the treating oncologist according to standard protocols of clinical care.

   Note: Subjects must either be 1) initiating their first systemic cancer therapy regimen based on initial diagnosis, 2) initiating their first cycle of a new systemic cancer therapy regimen for a recurrence, or 3) starting the first cycle of a new regimen of systemic cancer therapy based on tolerability or disease progression.

   Note: Every effort should be made to initiate systemic cancer therapy on the same day as the first dose of study drug or within 72 hours of the first dose of study drug when at all possible. However, subjects can continue in the study if there is a delay in initiation of systemic cancer therapy beyond +7 days after receiving the first dose of study drug.

7. Be medically stable on the basis of physical examination, medical history, and vital signs performed at screening (or within 14 days before randomization on Day 1). If there are abnormalities, they must be consistent with the underlying illness in the study population.

8. Criterion modified per Amendment-3

   8.1 Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

   If a woman, before entry she must be:

   postmenopausal (for at least 12 months), or surgically sterile (have had a total hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or practicing a highly effective method of birth control, if sexually active, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine

device, double-barrier method for less effective methods of contraception (eg, condoms, diaphragm, cervical cap, or sponge 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 trials, for the duration of their participation in the study, or not heterosexually active

Note: subjects who are not heterosexually active at screening must agree to utilize a highly effective method of birth control if they become heterosexually active during their participation in the study.

9. If a woman of childbearing potential, must have a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test at screening.

10. Criterion modified per Amendment-3

    10.1 If a man, must agree to use an adequate contraception method as deemed appropriate by the investigator (eg, vasectomy, condoms, partner using effective contraception).

11. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

12. Be able to provide informed consent and sign an informed consent document indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study. The subject will be excluded if he or she has a/an:

1. Diagnosis of primary brain tumors

2. Known history of brain metastases

3. Bleeding diathesis, hemorrhagic lesions, active bleeding, and other conditions with a high risk for bleeding

4. Hematologic malignancies with the exception of lymphoma

5. Life expectancy of ≤6 months

6. Significant comorbidities, that in the opinion of the treating physician would unnecessarily complicate participation in this clinical study, or provide excessive

clinical risk to the subject to participate in this clinical study

7. Diagnostically confirmed significant liver disease or dysfunction. Examples of significant liver disease include acute clinical hepatitis, chronic active hepatitis, or cirrhosis; examples of significant liver dysfunction as defined by liver function test (LFT) abnormalities (confirmed by repeat-testing) include:

   ALT >5x upper limit of normal (ULN)

   ALT >3x ULN plus total bilirubin >2x ULN and a ratio of direct to total bilirubin ≥50%.

8. Evidence of VTE on screening CU or incidental VTE identified on spiral CT scans ordered primarily for staging or restaging of malignancy ≤30 days prior to randomization

9. Platelet count <50,000/mm^3

10. Activated partial thromboplastin time (aPTT) >1.5 ULN or international normalized ratio (INR) >1.5

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

12. Concomitant use of anticoagulation therapy for prior VTE or other indications with either LMWH, warfarin, or direct oral anticoagulants

13. Criterion modified per Amendment-3

    13.1. P2Y12 receptor antagonist antiplatelet therapy (such as clopidogrel, prasugrel, and ticagrelor), daily nonsteroidal anti-inflammatory drugs, or other medications known to increase the risk of bleeding (a daily dose of ≤100 mg of aspirin is permitted)

14. Any condition (ie, atrial fibrillation) 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

15. Combined P-glycoprotein (P-gp) and strong cytochrome P450 (CYP) 3A4 inhibitors (such as but not limited to ketoconazole, telithromycin or protease inhibitors) use within 4 days before randomization, or planned use during the study. Itraconazole use within 7 days before randomization or planned use during the study.

16. Combined P-gp and strong CYP3A4 inducers (such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's Wort) use within 2 weeks before randomization, or planned use during the study.

17. Inability to take oral medication

18. Pregnant or breast-feeding or any plan to become pregnant during the study.

19. Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening and prior to randomization on Day 1. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

1. All women of childbearing potential must remain on a highly effective method of birth control (see inclusion criteria).

2. Criterion modified per Amendment-3.

   2.1 If a man, must agree to use adequate contraception method as deemed appropriate by the investigator (eg, vasectomy, condoms, partner using effective contraception).

3. Criterion modified per Amendment-3

   3.1 Subjects must not use mechanical thromboprophylaxis, such as pneumatic compression devices, foot pumps, for VTE prevention unless in a hospital setting. Compression stockings are permitted regardless of the setting.

4. A subject should not take any prohibited therapy. Refer to Section 8, Prestudy and Concomitant Therapy, for the full list of prohibited therapy. If a subject requires or takes prohibited medications during the study, they must either temporarily interrupt or permanently discontinue the study drug, as appropriate for the duration of the therapy with the prohibited medication.

5. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study (ie, concomitant medical conditions should continue to be treated appropriately).

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

5. TREATMENT ALLOCATION AND BLINDING

Randomization Procedures

A centralized randomization strategy will be implemented in this study. Subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups based on a computer-generated subject-randomization schedule prepared by or under the supervision of the sponsor prior to initiation of the study. The randomization will be stratified by tumor type (APC or non-APC) such that up to approximately 25% of the subjects randomly assigned are those with APC. Using the randomization schedule, the IWRS will assign treatment. The IWRS will also provide the number of the study drug bottle to be dispensed for each randomly assigned subject on Day 1 and at each visit (except Day 180/EOT) during the double-blind treatment period. Subjects will have up to 4 days to complete Day 1 from the point of being randomly assigned study drug within IWRS (date of randomization) to initiate their study drug treatment in order to accommodate those subjects who will be receiving their study drug from a centralized drug depot; however, every effort should be made to initiate study drug within 1 day. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then be asked to provide relevant subject details to uniquely identify the subject. Based on these randomization codes, the study drug will be packaged and labeled in a manner that maintains the double-blinded nature of this study.

Blinding

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

Data that may potentially unblind the treatment assignment (ie, events that contribute to the primary and secondary outcome or treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Unblinding

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be 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 telephoning 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 and reason for the unblinding must be documented in the appropriate section of the electronic case report form (eCRF), and 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 (eg, sealed envelope) so as not to unblind the treatment assignment to the study site or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the study site or sponsor personnel.

If a subject has a suspected efficacy or bleeding outcome event during the study, the treating physician should exercise clinical judgment and follow guidelines to apply the standard-of-care. Unblinding of study drug should not be necessary. Anticoagulation regimens do not require adjustment regardless of treatment group assigned when the study drug is administered in the dose used in this study. If despite this guidance, the investigator believes it is in the best interest of the subject to unblind study drug, the investigator may determine the treatment assignment or allocation by contacting the IWRS as previously noted.

Subjects who have had their treatment assignment unblinded may continue on study drug and will be expected to return for scheduled evaluations unless the subject meets a study drug temporary interruption or permanent 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. In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

An unblinded IDMC will periodically assess the safety date of subjects in the study and evaluate the efficacy data, as necessary. The IDMC will not be involved with the study otherwise. IDMC responsibilities and procedures are outlined in the IDMC charter.

6. DOSAGE AND ADMINISTRATION

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

- Rivaroxaban 10 mg orally once daily for 180 days.
- Placebo 10 mg orally once daily for 180 days.

Every effort should be made to initiate systemic cancer therapy on the same day as administration of the first dose of study drug, or within 72 hours of the first dose of study drug, when at all possible. However, for pragmatic reasons, subjects may be allowed to initiate systemic cancer therapy within a period of ±1 week prior to, or after their first dose of study drug, with a preference of this occurring within the first week following study drug administration, with the intention that systemic cancer therapy will continue during the double-blind treatment period for a duration determined by the treating oncologist according to

standard protocols of clinical care. Subjects that are screened and initiate systemic cancer therapy more than 1 week before the first dose of study drug should not be randomized and will be considered a screen failure. However, if a subject does not initiate systemic cancer therapy as planned within +1 week after the first dose of study drug, the subject is allowed to continue taking the study drug and remain in the study. The initial dose of study drug should be taken on Day 1 at a time that is most convenient for the subject. Subsequent doses of study drug should be taken every 24±2 hours, thereafter. The study drug can be taken with or without food and should be taken at the same time daily. For subjects who are unable to swallow whole tablets, tablets may be crushed and mixed with applesauce immediately prior to use and administered orally. In the event that a dose of study drug is missed, the missed dose should be taken as soon as possible. If a dose is missed, advise the subject to take the study drug as soon as possible on the same day and continue on the following day with their recommended daily dose regimen.

Throughout the study, study drug will be dispensed at appropriate intervals (see TIME AND EVENTS SCHEDULE) to ensure that subjects have adequate quantities of study drug between visits. In addition, study staff will instruct subjects on how to store the study drug for at-home use as indicated for this protocol. Study staff should also instruct subjects to bring the study drug with them to the hospital, if they need to be hospitalized for a reason that would not require temporary discontinuation of the study drug.

Refer to Section 9.3, Safety Evaluations, for additional information regarding interruption of study drug for bleeding events, Section 10.2.1, Temporary Discontinuation of Study Treatment, for circumstances requiring study drug to be temporarily discontinued, and Section 10.2.2, Permanent Discontinuation of Study Treatment, for circumstances requiring study drug to be discontinued.

7. TREATMENT COMPLIANCE

The investigator or designated study personnel will maintain a log of all drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects will return empty study drug containers and unused study drug at each visit when a new supply of study drug is to be received.

Subjects should report any unintentional interruptions or missed doses to the study-site personnel at each visit. It is understood that subjects may occasionally miss a dose of study drug. Additionally, subjects may have study drug temporarily discontinued for bleeding events as discussed in Section 9.3, Safety Evaluations, or in Section 10.2, Temporary Discontinuation of Study Treatment, for other circumstances.

8. PRESTUDY AND CONCOMITANT THERAPY

For prestudy and all concomitant therapies as described below, the identity, indication, dosage, and start and stop dates, when applicable, must be recorded in the eCRF.

Prestudy Therapies

Prestudy therapies are those administered within the 2 weeks before the first dose of study drug (Day 1). All prestudy therapies must be recorded in the eCRF except supplements such as fish oil, herbal medicines, and vitamins. The intent is to enroll subjects and begin the first dose of study drug before administration of systemic cancer therapy or radiotherapy; however, for pragmatic reasons subjects can be allowed to initiate systemic cancer therapy within a period of ±1 week prior to, or after their first dose of study drug, with a preference of this occurring within the first week following study drug administration.

Concomitant therapies are those administered after the first dose of study drug (Day 1).

All concomitant therapies taken throughout the double-blind treatment period for the treatment of AEs/serious adverse events (SAEs), prohibited medications, additional medications listed below, and systemic cancer therapy and radiotherapy must be recorded in the eCRF except supplements such as fish oil, herbal medicines, and vitamins. In addition, concomitant therapies should also be recorded beyond the Day 180/EOT visit only in conjunction with SAEs that meet the criteria outlined in Section 12.4.2, Serious Adverse Events.

Subjects will receive standard-of-care systemic cancer therapy at the discretion of the investigator or qualified designee.

- Use of other agents that may increase the risk of VTE must also be recorded in the eCRF (eg, erythropoiesis-stimulating agents).
- Nonsteroidal anti-inflammatory drugs (NSAIDs), excluding aspirin (a daily dose of ≤100 mg of aspirin is allowed), may be used on a temporary basis (ie, no more than 24 to 48 hours), but should be avoided for longer periods during treatment with the study drug, if possible.
- Medicines that reduce gastric acid (eg, H_2 antagonists or proton pump inhibitors) may reduce the incidence of gastrointestinal bleeding in subjects who are treated with anticoagulants in combination with NSAIDs and/or aspirin, and their concomitant use may be considered unless contraindicated.
- Changes to medications taken prestudy, and if ongoing at study entry, must be recorded in the eCRF.
- All systemic cancer therapy must be recorded in the eCRF.
- All radiotherapy must be recorded in the eCRF.

Prohibited Therapy

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

The following therapies are prohibited during the study:

- Fibrinolytic therapy
- Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin, or protease inhibitors) use within 4 days before randomization, or planned use during the study. Itraconazole use within 7 days before randomization or planned use during the study.
- Antiplatelet therapy
  - Aspirin >100 mg/day
  - P2Y12 receptor antagonists (eg, clopidogrel, prasugrel, ticagrelor)
  - Thrombin receptor antagonists (eg, vorapaxar)
- Daily use of NSAIDs, or other medications known to increase the risk of bleeding
- Anticoagulant (eg, warfarin sodium or other VKAs, Factor II or Xa inhibitors) is prohibited as concomitant therapy during the study. Study drug should be discontinued in subjects who develop any condition that requires anticoagulation or thromboprophylaxis. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study.

If a subject requires or takes prohibited medications during the study, he/she must either temporarily interrupt or permanently discontinue the study drug depending on the duration of the prohibited therapy (see Section 10, Subject Completion/Withdrawal), as appropriate for the duration of the therapy with the prohibited medication. Study drug may be restarted after the prohibited therapy has been discontinued and after completion of a suitable washout period at the investigator's discretion. During the post-treatment period, prohibited therapies may be administered, if required in the judgment of the investigator. If administered, these therapies must be recorded in the eCRF.

Thromboprophylaxis with mechanical devices (eg, pneumatic compression devices, foot pumps) is prohibited, unless in a hospital setting, because they could potentially interfere with the efficacy assessments.

Therapies to be Avoided

The following therapies should be avoided during the study:

- Combined P-gp and strong CYP3A4 inducers (such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's Wort) use within 2 weeks before randomization, or planned use during the study.

Prophylaxis of VTE Following Completion of Study Drug

The subject will be reminded to follow their healthcare provider's recommendations for their ongoing care plan for prophylaxis of VTE at the Day 180/EOT visit.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

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

Additional urine pregnancy tests may be performed for female subjects, 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 estimated total volume of blood to be collected for protocol-specified laboratory evaluations in this study is approximately 56.0 mL for each subject. The following table summarizes the estimated volume of blood to be drawn during the study.

Type of Sample	Volume per Sample (mL)	Samples per Subject During Study	Maximum Total Volume of Blood[a] (mL)
Clinical laboratory tests			
• Hematology	2.0	4	8.0
• Serum chemistry	2.5	4	10.0
• Coagulation	2.0	1	2.0
Biomarkers	8.5	4	34.0
Pharmacokinetic sample	2 mL	1	2
Total	n/a	n/a	56

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

9.1.2. Screening Phase

The Time and Events Schedule summarizes the safety and other measurements performed at the screening visit.

Subjects with various cancer types who are planned to receive systemic cancer therapy throughout the double-blind treatment period, and are judged by the investigator or qualified designee to be an appropriate candidate for thromboprophylaxis treatment based on their clinical status and Khorana thromboembolic risk score ≥2, will be screened for inclusion in the study.

Designated study personnel will explain the nature of the study, including all relevant details, and obtain written informed consent from the subject before initiation of any study-related procedures. Following the signing of the informed consent form (ICF), screening procedures will be completed no more than 14 days before Day 1 of the double-blind treatment period.

Subjects will be screened and randomized using laboratory results (see Note below) and local reader results for CU from testing performed within 14 days before randomization (Day 1) for the inclusion and exclusion clinical laboratory parameters and imaging requirements. Subjects

found to have baseline DVT on screening CU or incidental DVT or PE as identified from routine care imaging (eg, spiral CT scans ordered primarily for staging or restaging of malignancy) within 30 days prior to randomization will not be eligible for randomization. Subjects may be rescreened once, if not randomized after the initial screening. All screening procedures must be repeated if rescreening is performed after the initial 2-week screening period.

Note: If historical laboratory results (done per standard-of-care) are already available during the screening period (must have been previously drawn within 2 weeks of randomization), they may be used to determine eligibility. This will enable subjects to be screened and randomized on the same day. These historical laboratory results will be documented in the subject's source documents. In addition, subjects should still have all required safety laboratory tests drawn as per the Time and Events Schedule and sent to the central laboratory for analysis. In the event that the screening laboratory results from the central laboratory indicates the subject is not eligible then the historical laboratory results will take precedence and should be recorded in the eCRF to document eligibility.

Adverse events will be recorded from the time a signed and dated ICF is obtained until completion of the last study-related procedure. See Section 12, Adverse Event Reporting and Attachment 1, Reporting of Efficacy Endpoints, Adverse Events, and Serious Adverse Events.

9.1.3. Double-Blind Treatment Phase

The Time and Events Schedule summarizes the efficacy, safety, and other measurements performed at visits during the double-blind treatment period.

Day 1/Day of Randomization

If the subject meets all of the inclusion and none of the exclusion criteria, he or she is eligible to be randomly assigned to receive rivaroxaban or placebo. All screening activities must be completed before randomization and the results must be available to the investigator to review to ensure that no exclusion criteria are present. Subjects will be randomly assigned by an IWRS in a 1:1 ratio on Day 1 to receive double-blind treatment with either rivaroxaban 10 mg orally once daily or placebo 10 mg once daily for 180 days. The IWRS also will provide the number of the study drug bottle to be dispensed to subjects based on their randomized treatment. See Section 5, Treatment Allocation, for additional information on IWRS. Subjects will have up to 4 days to complete Day 1 from the point of being randomly assigned study drug within IWRS (date of randomization) to initiate their study drug treatment in order to accommodate those subjects who will be receiving their study drug from a centralized drug depot; however, every effort should be made to initiate study drug within 1 day.

Once randomly assigned, subjects will have study drug dispensed and will receive instructions on study drug dosing, as detailed in Section 6, Dosage and Administration.

At the randomization visit, before randomization occurs, site staff must review the visit schedule and the importance of completing the study with both the subject and any family members present. Randomization should not occur if the subject does not have transportation to study visits, or does not believe they will have sufficient support to comply with the protocol.

In addition, the importance of reporting signs and symptoms associated with bleeding, DVT and PE will be stressed. Subjects and family members, as appropriate, will be counseled on the signs and symptoms associated with DVT, PE, and bleeding.

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

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

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

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

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

Double –Blind Treatment Period (Day 1 -Day 180)

Subjects will have study visits performed at Week 8 (±7 days), Week 16 (±7 days), and at Day 180/EOT (±3 days) during the double-blind treatment period as outlined in the Time and Events Schedule. All study visits should be coordinated with subject's planned visits that are part of their standard-of-care, as long as the planned visits are within the protocol-specified visit windows. Either the PI (or a qualified subinvestigator) will be required to see each subject at every study visit for clinical assessment of the subject's status.

At each visit, the investigator or qualified designee will assess each subject for the occurrence of clinical events relevant to efficacy and safety endpoints, and if identified, will ensure that all necessary source documentation is collected to be forwarded to the independent blinded CEC as described in Section 9.2.1, Efficacy Evaluations and Outcomes. In addition, subject counseling on the signs and symptoms associated with DVT, PE, and bleeding provided at the randomization visit will be repeated in detail.

Subjects will be instructed to return unused study drug at each visit. The IWRS must be contacted at each visit (except Day 180/EOT) to obtain the number of the study drug bottles to be dispensed to each subject. Study personnel will reinforce the dosing schedule and procedure to follow if a dose is missed. See Section 5, Treatment Allocation, for additional information on IWRS.

Subjects will undergo mandatory CU at Week 8 (±7 days), Week 16 (±7 days) and Day 180 (±3 days). The Day 180/ EOT visit will be performed at the completion of 180 ±3 days of treatment with study drug (regardless of whether a subject is ongoing in a cycle of systemic cancer therapy). The CU planned for the Day 180/EOT visit will be conducted preferably on the day of the visit or within the visit window (Day 180 ±3 days) but must be performed before the last dose of study drug.

If a subject permanently discontinues the study drug before the end of the double-blind treatment period (Day 180 visit), he/she should be instructed to complete an unscheduled EOT visit as soon as possible from the time that the study drug was discontinued, and have the CU performed within 2 days of taking the last dose of study drug. At the unscheduled EOT visit, all procedures as outlined in the Time and Events Schedule will be performed. In addition, subjects that permanently discontinue study drug before the Day 180 visit will be required to complete all remaining study visits, including what would have been their Day 180/ EOT and Day 210/ EOS visits. If the unscheduled EOT visit falls within the window of a remaining study visit, the subject does not need to repeat this next scheduled study visit.

The investigator should inform subjects of the importance of returning for all study visits (regardless of duration of study drug treatment) as it is imperative for the integrity of the study and results to have vital status and other outcomes ascertainment. If the subject is unwilling or unable to return for any visits, or is lost to follow up, the investigator should collect as much follow-up information as possible for each remaining visit, including contacting the subject or legally acceptable representative by telephone or by mail to determine vital status and outcome ascertainment, as agreed to by the subject during the informed consent process. The site must document all attempts to try to contact the subject in the source documents. If applicable, vital status and other outcomes should be obtained by reviewing the subject's medical or public records unless this contact is not allowed by local regulations.

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

During the double-blind treatment period, study drug dosing may be interrupted as necessary for invasive procedures or as medically needed. Recommendations for temporary discontinuation of study drug for bleeding can be found in Section 9.3.1.1, Management of Study Drug for Bleeding Events.

Additional guidance on reporting of efficacy endpoints, AEs, and SAEs is presented in Section 9.2.1, Efficacy Evaluations and Outcomes, Section 12.4.1, All Adverse Events, Section 12.4.2, Serious Adverse Events, and Attachment 1, Reporting of Efficacy Endpoints, Adverse Events, and Serious Adverse Events.

9.1.4. Post-treatment Phase (Follow Up) (Day 181 – Day 210)

The Time and Events Schedule summarizes the efficacy, safety, and other measurements performed during the post-treatment period.

At the end of the post-treatment follow-up period (Day 210 visit), all subjects (or their legally acceptable representative), including those who discontinued the study drug prior to the Day 180 visit, will be contacted by telephone for a Day 210/EOS follow-up assessment and will have their vital status (eg, dead, alive, or lost-to-follow up) as well as any additional information available such as AEs, concomitant medications, bleeding events, and clinical events relevant to endpoints collected. All subjects will have Day 210/EOS procedures performed at this visit.

If the subject is lost-to-follow up, the investigator should collect as much follow-up information as possible for each remaining visit, including contacting the subject or legally acceptable representative by telephone or by mail to determine vital status and outcome ascertainment, as agreed to by the subject during the informed consent process. The site must document all attempts to try to contact the subject in the source documents. If applicable, vital status and other outcomes should be obtained by reviewing the subject's medical or public records unless this contact is not allowed by local regulations.

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

Additional guidance on reporting of efficacy endpoints, AEs, and SAEs is presented in Section 9.2.1, Efficacy Evaluations and Outcomes, Section 12.4.1, All Adverse Events, Section 12.4.2, Serious Adverse Events, and Attachment 1, Reporting of Efficacy Endpoints, Adverse Events, and Serious Adverse Events.

9.2. Efficacy Evaluations and Outcomes

9.2.1. Efficacy Evaluations and Outcomes

The following efficacy outcomes will be evaluated at the time points listed in the Time and Events Schedule:

- symptomatic lower extremity proximal DVT
- symptomatic upper extremity DVT
- asymptomatic lower extremity proximal DVT
- symptomatic lower extremity distal DVT
- confirmed fatal/non-fatal ATE events
- confirmed fatal/non-fatal visceral VTE events
- symptomatic non-fatal PE
- incidentally detected PE through restaging imaging
- VTE-related death
- all-cause mortality

The primary efficacy outcome variable is objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity

distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and VTE-related death.

The key secondary efficacy outcomes are:

- symptomatic VTE events (DVT/PE) and VTE-related deaths
- all-cause mortality.

Other secondary outcomes are:

- individual components of the primary efficacy composite variable
- confirmed fatal/non-fatal ATE events
- confirmed fatal/non-fatal visceral VTE events
- composite of symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and all-cause mortality
- composite of symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, and VTE-related death

An independent blinded CEC will apply the protocol definitions and adjudicate and classify safety and efficacy endpoint events.

The investigator will use all available source documents (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.

Investigators will ensure that all necessary source documentation is collected to be forwarded to the independent blinded CEC to enable event adjudication and verification. Source documentation should only contain subject number and initials, and care should be taken to obscure personal identifiers so that subject privacy is maintained.

Adjudicated results will be used for final analyses. In subjects who died during follow up, death certificates, and if available, autopsy findings will be reviewed to establish a diagnosis of fatal PE.

Additional information on reporting of clinical efficacy and safety endpoints is presented in Attachment 1, Reporting of Efficacy Endpoints, Adverse Events, and Serious Adverse Events.

9.2.1.1. Definitions

The following definitions will be applied by the independent blinded CEC based on objective confirmation.

Lower extremity proximal DVT

The adjudicated presence of a DVT located in the proximal veins of lower extremities (includes the external iliac vein, common femoral vein, superficial femoral vein, proximal part of the deep femoral vein, popliteal vein, and trifurcation area of calf veins), as evidenced by a positively diagnosed and adjudicated CU. If the CU is deemed to be of unsatisfactory quality, confirmation may be done by venography if ordered by the investigator or qualified designee. Asymptomatic events will include those subjects who are asymptomatic or otherwise unaware of and lack clinical signs for a DVT. Symptomatic events will include those subjects who are symptomatic or otherwise aware of and/or have clinical signs for a DVT.

Symptomatic lower extremity distal DVT

The adjudicated presence in subjects who are symptomatic or otherwise aware of and/or have clinical signs for a DVT located in the distal veins of the lower extremities, as evidenced by the final clinical diagnosis, including a positively adjudicated CU. If the CU is deemed to be of unsatisfactory quality, confirmation can be done by venography if ordered by the investigator or qualified designee. Asymptomatic lower extremity distal DVTs will not be included in endpoint data collection.

Symptomatic upper extremity DVT

The adjudicated presence in subjects who are symptomatic or otherwise aware of and/or have clinical signs for a DVT located in the veins of the upper extremities as confirmed by abnormal CU (includes but is not limited to the internal jugular vein, subclavian vein, axillary vein, brachial vein in the arm, cephalic vein in the arm, basilic vein in the arm, paired ulnar, radial, and interosseous veins in the forearm).

This includes thrombosis of the central line when the subject presents with symptoms (eg, swelling, erythema, pain, distal paresthesia, neck swelling, headache, congestion of subcutaneous collateral veins)

Symptomatic non-fatal PE

The adjudicated presence in subjects who are symptomatic or otherwise aware of and/or have clinical signs for a PE objectively confirmed by CT scan.

Incidental PE

Venous thromboembolism in pulmonary arteries identified on scans ordered primarily for staging or restaging of malignancy or otherwise conducted for reasons other than the identification of PE, with CT scan utilizing 5 mm slice thickness or less.

VTE-related death

An adjudicated death attributed, by the investigator, to the occurrence of a fatal VTE event.

Visceral VTE

Thrombi formed in portal, splenic, superior mesenteric, inferior mesenteric, hepatic, gonadal, renal veins, or inferior vena cava as evidenced by CT scan.

Any ATE

The adjudicated presence of a final clinical diagnosis of thrombosis/thromboembolism diagnostically confirmed, including myocardial infarction, stroke, peripheral arterial disease, and involving the following arterial vascular beds: carotid, upper or lower extremity, gastrointestinal tract, liver, spleen, or kidney.

All-cause mortality

All-cause mortality includes all deaths.

9.2.2. Efficacy Endpoints

The primary efficacy composite endpoint is the time from randomization to the first occurrence of objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, or VTE-related death occurring from randomization to the Day 180 visit as adjudicated by the independent blinded CEC.

The key secondary efficacy endpoints include the following: 1) symptomatic VTE events (DVT/PE) and VTE-related deaths and 2) all-cause mortality from the time of randomization to the Day 180 visit.

Other secondary efficacy endpoints include the time from randomization to the first occurrence for the following events during the 180-day, double-blind treatment period, defined as:

- individual components of the primary efficacy composite variable analyzed separately
- confirmed fatal/non-fatal ATE events
- confirmed fatal/non-fatal visceral VTE events
- composite of symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE and all-cause mortality
- composite of symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, and VTE-related deaths.

9.2.3. Approach to the Subject with an Efficacy Outcome Event

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

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

9.3. Safety Evaluations

Details regarding the IDMC are provided in Section 11.9.2, Independent Data Monitoring Committee.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be managed by the investigator and other treating physicians as a part of standard-of-care.

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

9.3.1. Bleeding Events

The primary safety objective of this study is to assess the major bleeding events as defined by ISTH from the time of randomization to 2 days after the last dose of study drug. Secondary safety endpoints include the proportion of clinically relevant non-major bleeding, minor bleeding, any bleeding (defined as major, clinically relevant non-major, and minor bleeding as defined by ISTH). Similar to efficacy outcomes, the same independent blinded CEC will adjudicate and classify bleeding events (major and clinically relevant non-major) according to the definitions in the CEC charter. Details of all bleeding events will be captured in the eCRF.

Bleeding events will be classified as major, clinically relevant non-major, or minor bleeding as follows:

Major bleeding

Major bleeding is defined as clinically overt bleeding that is associated with:

- A reduction in hemoglobin of 2 g/dL or more, or
- A transfusion of 2 or more units of packed RBCs or whole blood, or
- Occurrence at a critical site defined as intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- Fatal outcome

Clinically relevant non-major bleeding

Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with:

- Medical intervention
- Unscheduled contact (visit or telephone call) with a physician
- Temporary cessation of study treatment, or
- Discomfort such as pain, or impairment of activities of daily life

Examples of clinically relevant non-major bleeding are:

- Epistaxis that lasts longer than 5 minutes, is repetitive (2 or more episodes of true bleeding [ie, more than isolated drops of blood or simply blood-spotting on a tissue or handkerchief] within 24 hours), or that requires an intervention (eg, packing, electrocautery)
- Gingival bleeding that occurs spontaneously (ie, unrelated to tooth brushing or eating), or lasts longer than 5 minutes
- Hematuria that is macroscopic, and either spontaneous or lasts longer than 24 hours after instrumentation (eg, catheter placement or surgery) of the urogenital tract
- Macroscopic gastrointestinal hemorrhage: at least 1 episode of melena or hematemesis, if clinically apparent
- Rectal blood loss, if more than a few drops of blood
- Hemoptysis, if more than a few streaks or specks of blood in the sputum
- Intramuscular hematoma without compartment syndrome
- Subcutaneous hematoma if larger than 25 cm^2 in general or 100 cm^2 if provoked
- Multiple-source non-major bleeding

Minor bleeding

All other overt bleeding episodes not meeting the criteria for major or clinically relevant non-major bleeding will be classified as minor bleeding.

9.3.1.1. Management of Study Drug for Bleeding Events

For clinically significant (major and relevant non-major) bleeding events, the study drug should be stopped or the subject managed according to the guidelines below. The decision to restart or permanently withdraw study drug after resolution of a bleeding event will be made by the investigator and must be documented.

If a subject has a clinically significant bleeding event during study treatment, the following routine measures could be considered:

- Delay the next study drug administration, or discontinue treatment if appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours; depending on factors, including

age, etc. Therefore, temporary cessation of study drug may be sufficient to establish control of bleeding.

- Appropriate examinations and symptomatic treatment, (eg, mechanical compression [eg, for severe epistaxis], surgical interventions, as appropriate, fluid replacement and hemodynamic support, blood product or component transfusion) should be considered.
- Also consider that other causes besides antithrombotic medication can be contributory to the seriousness of the bleeding event (eg, rule out disseminated intravascular coagulation, thrombocytopenia, other coagulopathies, kidney and liver dysfunction, concomitant medications), and treat accordingly.

If bleeding cannot be controlled by the above measures, consider administration of one of the following procoagulants according to the dosages advised in the package insert:

- activated prothrombin complex concentrate
- prothrombin complex concentrate
- recombinant factor VIIa

However, there is currently no experience with the use of these products in individuals receiving rivaroxaban. Any products administered to control bleeding should be entered in the eCRF.

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

9.3.2. Other Safety Assessments

9.3.2.1. Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures. Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

9.3.2.2. Clinical Laboratory Tests

Subjects will be screened and randomized using central laboratory results from testing performed within 14 days before randomization (Day 1) for the inclusion and exclusion clinical laboratory parameters. If historical laboratory results (done as per standard-of-care) are already available during the screening period (must be previously drawn within 2 weeks of randomization), they may be used to determine eligibility. This will enable subjects to be screened and randomized on the same day. These historical laboratory results will be documented in the source

documentation. In addition, subjects should still have all required screening labs drawn as per the Time and Events Schedule and sent to the central laboratory for analysis. In the event that the screening laboratory results returned from the central laboratory indicates the subject is not eligible, then the historical laboratory results will take precedence and should be entered into the eCRF to document subject eligibility.

Blood samples for hematology and serum chemistry will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

The following tests will be performed:

- Hematology Panel: hemoglobin, hematocrit, RBC, WBC count with differential, and platelet count
- Serum Chemistry Panel: sodium, potassium, chloride, bicarbonate, BUN, glucose, uric acid, calcium, phosphate, albumin, total protein, creatinine (for calculation of CrCl), AST, ALT, total and direct bilirubin, and alkaline phosphatase
- Urine Pregnancy Testing will be performed at the screening and at the Day 180/EOT visit for women judged by the investigator to be of childbearing potential only. The protocol-specified sample for urine pregnancy testing must be collected before randomization. If, subsequently, the results are positive for pregnancy, the subject should be discontinued from the study drug as soon as possible and should enter the post-treatment follow-up period. See Section 12.4.3, Pregnancy, for information on reporting pregnancy to the sponsor. Additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy before administration of the study drug and throughout the study.

9.3.2.3. Vital Signs

Vital Signs (oral or tympanic temperature, automated pulse, manual respiratory rate, automated blood pressure)

Blood pressure and pulse rate will be measured after subjects have been semi-recumbent for 5 minutes. Blood pressure and pulse rate measurements will be assessed with a completely automated device consisting of an inflatable cuff and an oscillatory detection system. All values will be registered on a built-in recorder so that measurements are observer-independent.

9.3.2.4. Medical History and Physical Examination

The targeted medical history and physical examination (including weight, height, and BMI) performed at screening should be obtained and performed in a manner that facilitates the investigator's ability to make reasonable evidence-based clinical assessments and decisions throughout the study related to the following circumstances and/or conditions that are related to the safety evaluations described in this section or to the assessment of the efficacy evaluations described in Section 9.2.1, Efficacy Evaluations:

- Vital signs
- Functional performance status
- Risk or presence of thromboembolism
- Risk or presence of bleeding including hematology status
- Liver function status and changes thereof
- Renal function status and changes thereof
- Status of study endpoints, including safety
- Potential presence of thrombophilia, if suspected
- Acute changes in the subject's clinical status

9.4. Biomarkers

9.4.1. Evaluations

Biomarkers related to inflammation and hypercoagulability will be assessed. Biomarker samples will be collected at the time points indicated in the Time and Events Schedule. The data will be used to quantitate circulating levels of D-dimer, P-selectin, and Tissue Factor.

9.5. Pharmacokinetics

9.5.1. Pharmacokinetic Sample Collection and Handling

At Week 8, blood samples will be taken to determine study drug concentrations. Subjects will attend the clinic for their regularly scheduled visit, before taking their study drug. Only 1 PK sample will be drawn immediately before study drug intake. Exact times of blood sampling and last 2 intakes of study drug will be recorded in the eCRF. All samples will be collected and processed according to the central laboratory's instruction manual. Handling and shipment of the samples and the materials will also be described in the manual.

9.5.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of rivaroxaban using a validated, specific, and sensitive liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method under the supervision of the sponsor's Bioanalytical Laboratory Department of Bioanalysis.

9.5.3. Pharmacokinetic Parameters

Rivaroxaban predose concentration at Week 8 will be summarized by descriptive statistics. Rivaroxaban PK parameters including AUC_{0-24}, C_{max} after single dose and AUC_{0-24}, C_{max}, and minimum plasma concentration (C_{min}) at steady state may be derived through model-based methods. When appropriate, PK data collected in this study may be pooled with data from other studies to reduce the uncertainty in the analysis. Relationship of efficacy and safety endpoints versus rivaroxaban exposure will be explored by graphical analysis and, if a trend is suggested

by graphical analysis, followed by quantitative analysis. Results from PK modeling and exposure-endpoint analyses will be reported separately from the clinical study report.

9.6. Health Care Resource Utilization

Health care resource utilization (HCRU) data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study.

Health care resource utilization data will be collected as part of the endpoint assessments, at Weeks 8 and 16, and Day 180/EOT, for all subjects and compared between the treatment groups, or until study drug discontinuation. The data collection will be specific to the study outcomes of DVT, PE, or bleeding, including visits to health care providers, hospitalization, length of hospitalization, and use of diagnostic procedures.

9.7. Other Evaluations

Functional Status

The functional status of the subjects will be assessed using the ECOG performance status scale (see Attachment 4, Functional Status Assessment Tool).

9.8. Sample Collection and Handling

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

For those blood samples collected for exploratory biomarker evaluation, instructions on sample collection, labeling, handling, and shipment will be provided in the laboratory manual.

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

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the double-blind treatment period if the subject continues taking the double-blind study drug until the Day 180 visit as well as has completed all study-related assessments.

A subject will be considered to have completed the study if the subject (regardless of whether he/she continues on study drug) is followed according to the visit schedule until the Day 210/EOS visit.

A subject will be considered to have not completed the study if the subject does not complete all study visits according the visit schedule until the Day 210/EOS visit.

All feasible efforts and measures will be made to collect complete vital status and other outcome data from randomization to the Day 180 visit for each subject randomized in this study,

regardless of compliance with study drug or visits. For subjects who are lost-to-follow up or withdraw consent from the study, efforts will be made to obtain their vital status and other outcomes from permitted sources.

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

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the double-blind treatment 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.

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

10.2.1. Temporary Interruption of Study Treatment

The study drug may be temporarily interrupted; however, these interruptions should be kept to a minimum as much as possible. If the subject misses more than 14 consecutive days of study drug, he/she will need to permanently discontinue the study drug. It is recommended, when possible, that the study drug be discontinued at least 24 hours, and at the discretion of the investigator, before an invasive procedure (ie, surgical) to reduce the risk of bleeding. In deciding whether a procedure should be delayed at least 24 hours after the last dose of study drug, the increased risk of bleeding should be weighed against the urgency of intervention. In case of major surgery or major bleeding risk procedure, the investigator may consider holding the prior day's dose of study drug (skip both doses of the study drug the day before and the day of surgery), weighing the risk of bleeding against that of VTE. Consider bridging with parental anticoagulation, if necessary. The study drug should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short. The investigator may consider resuming the study drug 24 hours after achieving hemostasis for low-bleeding risk or minor surgical procedures, and at 48 hours in case of major or high-risk bleeding procedures, noting that the time to onset of therapeutic effect is short.

During planned or emergency hospitalization, the study drug should be stopped only if the treating clinician determines that thromboprophylaxis or anticoagulation should be administered. It might be necessary to interrupt the study drug temporarily (eg, while a contraindicated mediation is taken). Subjects should resume the study drug as soon as it is deemed safe by the treating clinician, and study drug interruption during the treatment period should not exceed 14 consecutive days.

Study drug should be temporarily discontinued if the subject:

- Develops a new neurologic deficit or significant alteration in mental status.
- If the platelet count decreases to <25 x 10^9/L for more than 1 week, the subject will be temporarily discontinued until the platelet count returns to ≥25 x 10^9/L. Subjects should have their platelet count monitored carefully if the platelet count decreases to <50 x 10^9/L and investigator discretion should be used.
- Has a SAE that is considered by the investigator to be possibly related to, or exacerbated by, study drug administration.
- Requires any of the following prohibited therapies on a temporary basis:
  - Fibrinolytic therapy
  - Combined P-gp and strong CYP3A4 inhibitors (such as but no limited to ketoconazole, telithromycin, or protease inhibitors)
  - Antiplatelet therapy
    - Aspirin>100 mg per day, P2Y12 receptor antagonists (eg, clopidogrel, prasugrel, ticagrelor)
    - Thrombin receptor antagonists (eg, vorapaxar)
  - Daily use of NSAIDs, or other medications known to increase the risk of bleeding
  - Anticoagulants (eg, warfarin sodium or other VKAs, Factor II or Xa inhibitors)
- Experiences a major bleeding event. For less severe bleeding events, investigator discretion is allowed. If possible, the study drug should be resumed when the bleeding event has resolved and the cause has been identified and corrected (see Section 9.3.1.1, Management of Study Drug for Bleeding Events).
- Subjects should have their renal function monitored when CrCl drops below <30 mL/min and investigator discretion should be used with regard to study drug administration. If the subject's CrCl decreases to <15 mL/min, the subject should be discontinued from study drug treatment.

The study drug can be resumed when the investigator considers it safe to do so. If more than 14 consecutive days of study drug are missed, the subject will permanently discontinue the study drug and have an unscheduled EOT visit performed.

Subjects who have the study drug discontinued will be reminded to follow their healthcare provider's recommendations for their ongoing care plan for prophylaxis of VTE at the unscheduled EOT visit (see Section 8, Prestudy and Concomitant Therapy).

10.2.2. Permanent Discontinuation of Study Treatment

If a subject must be permanently discontinued from the 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's study drug treatment will be permanently discontinued if:

- At their own request, or at the request of their legally acceptable representative, without giving reasons (even though providing a reason is encouraged).
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
- At the specific request of the sponsor (exceptional circumstances).
- The subject develops a condition that requires anticoagulation or thromboprophylaxis extending beyond 14 consecutive days (see Section 10.2.1, Temporary Interruption of Study Treatment).
- The subject's calculated CrCl is <15 mL/min.
- The subject misses more than 14 consecutive days of study drug.
- The subject becomes pregnant.
- If the subject experiences an endpoint event, including a clinically significant bleeding event, at the treating physician's discretion, the routine measures described below may be considered.
  - Temporarily interrupt (not more than 14 consecutive days) or permanently discontinue study drug treatment as clinically indicated. If a subject experiences a VTE event, unblinding of study drug should not be necessary, as anticoagulation regimens do not require adjustment regardless of treatment group assigned when study drug is administered in the doses used in this study. If a subject has a serious bleeding event during study drug treatment, routine measures should be considered as described in Section 9.3.1.1, Management of Study Drug for Bleeding Events. If these measures are sufficient to stop bleeding, unblinding of study drug should not be necessary. If despite this guidance, the investigator believes it is in the best interest of the subject to unblind the study drug, the investigator may determine the treatment assignment or allocation by contacting the IWRS as previously noted.
  - Perform necessary diagnostic procedures and consider the usual treatment measures for VTE and/or arterial ischemic events if physical examination and diagnostic testing suggest benefit could be obtained.
  - After clinical evaluation of the suspected efficacy outcome event is completed, restarting the study drug may be considered if none of the conditions requiring permanent discontinuation noted above are present.

Early permanent discontinuation of study drug is discouraged wherever possible. The single most important reason for premature discontinuation should be marked on the appropriate eCRF and in the subject source documents. Subjects missing more than 14 consecutive days of taking the study drug will be discontinued from further study drug treatment and will not be restricted from seeking appropriate medical care available outside the protocol, but will be encouraged to make every effort to continue with their scheduled study visits until the planned end of their study duration. Discontinued subjects will not be replaced. Subjects who permanently discontinue the study for any reason will not be re-enrolled into the study.

If a subject permanently discontinues the study drug before the end of the double-blind treatment period (Day 180 visit), he/she should be instructed to complete an unscheduled EOT visit as soon as possible from the time that the study drug was discontinued, with the CU performed within 2 days of taking the last dose of study drug. In addition, the subject will be required to complete all remaining study visits and procedures including what would have been their Day 180/EOT and Day 210/EOS visits (see TIME AND EVENTS SCHEDULE). If the unscheduled EOT visit falls within the window of a remaining study visit, the subject does not need to repeat this required study visit.

The subject is required to return for all subsequent site visits and procedures until the Day 210/EOS visit. The investigator should inform the subject of the importance of returning for all study visits as it is imperative for the integrity of the study and results to have ongoing ascertainment of outcome event and vital status. If the subject is unwilling or unable to return for any visits, or is lost-to-follow up, the investigator should collect as much follow-up information as possible for each remaining visit, including contacting the subject or legally acceptable representative by telephone or by mail to determine vital status and outcome ascertainment, as agreed to by the subject during the informed consent process. In that respect, the investigator should ask the subject at the study start for the contact details of a relative or a friend who can be contacted in case the subject cannot be reached. The site must document all attempts to try to contact the subject in the source documents. In the event a subject withdraws consent and does not agree to any kind of follow up and specifically refuses any further contact with the investigator, 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. If applicable, the vital status and other outcomes will be obtained at study end through public information (death registries or other registries) according to local guidelines and as allowed by local regulations.

A decision to stop recruitment and/or study treatment can be taken by the EC following advice on safety aspects of study by the IDMC. The Independent Ethics Committee/Institutional Review Board (IEC/IRB) will be informed of the decision. Stopping guidelines will be defined prior to the start of the study. The sponsor has the right to close this study, and the investigator/the sponsor has the right to close a center, at any time, although this should occur after consultation between involved parties and the EC. The IEC/IRB must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at the

site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.

10.2.3. Medication Transition Management

Subjects who experience a primary or secondary study endpoint of objectively confirmed symptomatic lower extremity DVT, upper extremity DVT, non-fatal PE, asymptomatic proximal DVT of the lower extremity, incidental PE, and VTE-related death, confirmed non-fatal ATE events, and confirmed non-fatal visceral VTE events or any other thrombotic event that in the judgment of the treating physician will require antithrombotic treatment during the double-blind treatment period will have study drug discontinued and receive treatment per physician discretion.

- Switching study therapy with other anticoagulants
    - If switching blinded therapy to an anticoagulant with a rapid onset, discontinue study therapy and give the first dose of the other anticoagulant (oral or parenteral) at the time that the blinded treatment dose would have been taken.
    - When switching back from a rapid onset anticoagulant (eg, LMWH or non-warfarin oral anticoagulant) after a temporary discontinuation, start blinded study therapy 0 to 2 hours prior to the next scheduled administration of the drug and omit administration of the other anticoagulant.
    - For those subjects taking VKA for a temporary discontinuation who will be switched back to study therapy discontinue warfarin and start blinded study therapy as soon as the INR is below 3.0 to avoid overlapping anticoagulation and increased bleeding risk.
    - When switching from study therapy to VKA discontinue blinded therapy and begin both a parenteral anticoagulant and warfarin at the time the next dose of study drug would have been taken.

10.2.4. 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, where permitted by law, up until the Day 210/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 Day 210/EOS visit)
- Death

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. Outcome events and vital status data are crucial to the statistical analysis and must be collected until the end of the study even if subjects are no longer taking the study drug. Every effort will be made to contact any subject who is lost-to-follow up or withdraws consent and collect information on the occurrence of efficacy and safety endpoint

events and vital status, including a review of the subject's medical or public records unless this contact is not allowable by local regulations.

11. STATISTICAL METHODS

Statistical analysis will be performed 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 (SAP).

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

- Null hypothesis H0: there is no difference between treatments in distribution of time from randomization to the first occurrence of the primary efficacy composite endpoint event.
- Alternative hypothesis HA: The distributions of time from randomization to the first occurrence of the primary efficacy composite endpoint event are different between the 2 treatment groups.

In this study, data collected on the primary efficacy, safety, as well as the key secondary endpoints will be summarized across treatment groups. Specific imputation rules for missing data (eg, missing event dates) will be applied, if warranted, and will be specified in the SAP before final database lock. Descriptive statistics such as mean, median, standard deviation, interquartile range, minimum, and maximum will be used to summarize continuous variables. Counts and proportions will be used to summarize categorical variables. Graphical data displays (eg, box plots) may also be used to summarize data. Kaplan-Meier estimates adjusted for competing risk over time will be summarized and plotted for time-to-event variables.

11.1. Analysis Populations and Observation 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) *observation period*, which specifies the time window within which data will be included in an analysis. Key subject populations and observation periods are defined below.

Subject Population

Intent-to-treat (ITT) population: This subject population consists of all randomized subjects.

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 SAP.

Safety population: this population is a subset of the ITT population, consisting of all randomized subjects who receive at least 1 dose of study drug.

Observation Periods

Up to Day 180-visit: this observation period includes all data from randomization to the Day 180 visit, inclusive. For time-to-event analyses, subjects who do not experience endpoint

events during this period will be censored at the Day 180 visit or at the last day of their completed unscheduled EOT assessments for study outcomes during the treatment period, whichever occurs first.

On-treatment: this observation period includes data from the first dose of study drug to 2 days after the last dose of the study drug, inclusive. For time-to-event analyses, subjects who do not experience endpoint events during this period will be censored on the last dose date +2 days or at the last day of their completed unscheduled EOT assessments for study outcomes during the treatment period, whichever occurs first.

Post-randomization: this observation period includes all data from randomization to the last contact (ie, up to Day 210-/EOS visit).

Post-first dose of study drug: this observation period includes all data from the first dose of study drug to the last contact (ie, Day 210-/EOS visit).

11.2. Sample Size Determination

This is a 6-month, fixed-duration study to demonstrate the superiority of rivaroxaban compared with placebo in ambulatory cancer subjects undergoing systemic cancer therapy.

Estimates for VTE events in this population vary but in most studies, the data demonstrate a significant benefit (or, reduction in events) over placebo when cancer subjects are treated with anticoagulant therapy. According to a recent review of the VTE prophylaxis studies in cancer subjects by Khorana et al, the majority of RCTs on solid tumors have reported relative risk reductions (RRRs) anywhere between 50% and 64%. The duration of the earlier primary VTE prophylaxis studies in cancer was generally between 3 to 4 months, in conjunction with initiation of systemic anticancer therapy. The basis for predictive events is derived from the Vienna CATS group,[4] which utilized the Khorana thromboembolic risk score, and followed 819 ambulatory cancer subjects for symptomatic VTE as an endpoint. In a Kaplan-Meier analysis, the cumulative probability of VTE after 6 months: Khorana thromboembolic risk score ≥3, 17.7% (95% CI: 11.0%-27.8%, N= 93), and 9.6% (95% CI: 6.2%-14.7%, N=221) in those subjects with a Khorana thromboembolic risk score of 2. Taken together, these results, along with a number of smaller epidemiologic studies, in general support a symptomatic VTE rate at 180 days of at least 9.5% in subjects with a Khorana thromboembolic risk score of >2. The adjudication of objectively confirmed asymptomatic DVT and PE is estimated to add an additional 5% to 10% to the primary efficacy composite endpoint; therefore, an overall primary efficacy composite endpoint event rate of approximately 14.5% seems reasonable. Furthermore, it is assumed that the use of rivaroxaban will reduce this event rate to approximately 6.0%.

An independent blinded CEC, as described in Section 11.9.3, Clinical Endpoint Committee will apply the protocol definitions and adjudicate and classify safety and efficacy endpoint events, including major bleeding and clinically relevant non-major bleeding.

Based on the above information and recommendations from the Cancer-Associated Thrombosis Advisory Council, the sponsor planned the duration of the thromboprophylaxis treatment in the

multiple malignancy study up to 6 months. Therefore, the estimates of assumed events rates are relatively conservative given that the period of treatment follow up is longer than earlier RCTs.

In this study, with a 6-month planned treatment with rivaroxaban, the primary efficacy outcome variable is a composite of any symptomatic DVT, proximal asymptomatic DVT, any PE, and VTE-related death. The study design allows for a fixed treatment duration of 6 months on each successfully randomized subject. Assuming a cumulative incidence rate of 14.5% for the primary efficacy composite events in the placebo group and 6.0% cumulative incidence rate in the rivaroxaban treatment group, a total sample of about 700 randomized subjects (350 per treatment group) will be required to demonstrate approximately 60% RRR in the primary efficacy composite endpoint with a 2-sided Type 1 error rate of 5% and >90% statistical power (calculation performed by EaST 6.3 software), assuming a 20% discontinuation rate. Towards the end of the enrollment phase, approximately 800 subjects were planned to be randomized into the study due to the high subject discontinuation rate. In addition, this sample size will allow for 80% statistical power in each stratum (APC or non-APC) for slightly larger differences in incidence rates between the 2 randomized treatment groups to be statistically significant.

Essentially, the above overall sample size estimate is calculated based on the following assumptions:

- Effect size: absolute difference in event rates = 8.5%, RRR = 58.6%
  - Primary efficacy composite endpoint event rate in the placebo arm: 14.5%
  - Primary efficacy composite endpoint event rate in the rivaroxaban arm: 6%
- Power: >90%
- Overall α level: 5%, 2-sided
- Probability of dropping out of the study: 20%
- Duration of enrollment period: 12 months
- Duration of study: 6 months (fixed for each randomized subject)

11.3. Handling of Missing Data

For both the efficacy and safety endpoints, extensive efforts will be made to collect complete event and vital status data for all subjects randomized in this study. The number of subjects with missing follow up and the percentages of missing follow-up times will be summarized. Specific imputation rules will be applied to the missing data (eg, missing event dates). Sensitivity analyses will be conducted to assess impact of missing data on study results. Details will be provided in the SAP.

11.4. Interim Analysis

No interim efficacy analysis is planned in this study. An unblinded IDMC has been established for this study to periodically assess the safety of subjects in the study and evaluate the efficacy data, as necessary. For lower than expected numbers of primary events and/or significantly higher numbers of dropouts from the study, a blinded sample size re-estimation will be specified

in the SAP. Details of the IDMC roles, responsibilities, and key activities/timelines are provided in the IDMC charter.

11.5. Efficacy and Safety Analyses

The primary efficacy and key secondary endpoint analyses in this study will be based on the ITT population. All safety endpoints will be analyzed based on the safety population. Statistical tests will be based on a 2-sided Type 1 error rate of 5%. No adjustment in p-values for multiplicity of testing will be made unless otherwise specified. Associated 95% CIs will be provided. Primary and secondary events will be adjudicated by the independent blinded CEC and analyses will be based on these adjudicated events. Investigator-reported events will also be summarized. Additional data analyses (including those based on specific subgroups) will be identified in the SAP.

Primary efficacy composite endpoint analysis

The primary efficacy composite endpoint is the time from randomization to the first occurrence of objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, or VTE-related death during the observation period up to the Day 180 visit. The associated statistical null hypothesis is that there is no difference between treatment groups in distribution of the time to primary efficacy composite event, 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 tumor type (ie, APC vs. non-APC).

The primary efficacy composite endpoint analysis will be performed using a stratified Cox proportional hazard model (stratification factor: APC or non-APC), including treatment group as a categorical explanatory variable with 2 levels (ie, rivaroxaban, placebo) and will be based on the ITT population. Subjects who have no primary efficacy outcome during this observation period, or subjects who are lost to follow-up, or subjects who die because of other reasons than VTE, or subjects who withdraw informed consent before the end of the predefined treatment duration, will be censored at the last day of their complete assessment for study outcomes during the treatment period (assuming these types of censorings are independent of the primary outcome). Further details will be specified in the SAP. Subjects will be analyzed according to the treatment group to which they are randomized, regardless of actual treatment received.

To control the family-wise Type I error rate at alpha of 0.05 (2-sided) in testing for efficacy outcomes, if superiority of rivaroxaban over placebo on the primary efficacy outcome is established, superiority of rivaroxaban over placebo on secondary outcomes will be tested sequentially using a closed testing procedure in the following hierarchical order, each at alpha of 0.05 (2-sided):

- symptomatic VTE events + VTE-related deaths;
- all-cause mortality.

For each of these key secondary endpoint analyses, a Cox proportional hazard model with treatment and stratification factor as covariates will be employed. A point estimate along with 2-sided 95% CI for the treatment effect of RRR (RRR=100 x [1-HR] %) will be provided. The proportional hazards assumption will be assessed by visually comparing the plot of the log of cumulative hazard between treatments, and, if required, will be tested by appropriately including a treatment by log-transformed time interaction term in the Cox' model. Other secondary endpoints will be analyzed in similar fashion. 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.

A number of sensitivity analyses will be conducted to assess the robustness of the primary efficacy analysis by subgroups. These will include summarizing the incidence of symptomatic events and asymptomatic events by treatment group. An unstratified log-rank test will be used by repeating analyses mentioned above for different analysis sets and analysis observational periods. 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.

Homogeneity of treatment effects will be evaluated using the statistical model described above with treatment only as a covariate for the key subgroups listed below:

- Age (18 to <65 vs ≥ 65 years)
- Gender (men vs women)
- Tumor type (APC vs non-APC)
- Stage of disease (I-II vs III-IV)
- Khorana Score (<2, 2, and >2)
- ECOG score (0-1 vs 2 and above)
- Race (White or Caucasian, Black or African American, Asian, Other)
- Weight (<50 kg, >50 kg)
- Cancer types (eg, stomach, lung, lymphoma, renal, bladder, gynecologic, testicular)
- Geographic region (North America, Western Europe, Other)
- CrCl (30 to <50, 50 to <80, ≥80 mL/min)

To account for competing risks (deaths from causes other than VTE for efficacy, or fatal bleeding for safety) in the primary efficacy and safety analyses, a cumulative incidence approach will be followed with the use of Gray's 2-sample test (2-sided Type 1 error rate of 5%). Associated HRs and 95% CIs will be calculated with the use of the Fine and Gray regression model. Cumulative incidence functions will be estimated separately for the 2 randomized treatment groups. Additional statistical details of the specific models and inferential procedures to be used will be described in the SAP.

Key secondary efficacy endpoints will be analyzed in a similar fashion as the primary efficacy endpoint.

11.5.1. Safety Endpoints, Laboratory, and Vital Signs Data Analysis

The primary safety endpoint includes time to a major bleeding event in treated subjects in each randomized treatment group as defined by ISTH. A statistical comparison of the 2 randomized treatment groups will be performed using a stratified Cox's proportional hazards model with treatment as a covariate. Additionally, the frequency of bleeding events in each treatment group will be summarized. Secondary safety endpoints defined by percentages of clinically relevant non-major bleeding events will also be summarized. All reported AEs (ie, treatment-emergent adverse events [TEAEs], AEs that have worsened since baseline) will be summarized.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe AE or SAE. Laboratory data will be summarized and descriptive statistics for vital signs will be provided.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

11.6. Biomarker Analyses

Biomarker data will be summarized by treatment group and time point.

11.7. Pharmacokinetic Analysis

Descriptive statistics will be calculated for the plasma concentrations of the study drug at Week 8 and the derived PK parameters. Statistics include sample size (n), mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum.

11.8. Health Care Resource Utilization

The statistical analytic methods for the HCRU data will be further specified in the SAP. The HCRU data will be analyzed by treatment group with non-parametric methods for categorical variables, and log-transformation for continuous variables.

11.9. Committees

The EC, CEC, and IDMC responsibilities, authorities, and procedures will be documented in their respective charters.

11.9.1. Executive Committee

An EC will be formed that has overall responsibility for the conduct and reporting of the study. In addition, the EC will receive recommendations from the IDMC regarding safety analyses or modifications to the study. The EC will ultimately decide whether to accept the recommendations and will oversee the implementation of any modifications. Details of the composition, roles, and responsibilities will be documented in its charter. The members of the EC will be sponsor representatives identified by the study team and will include at least 2 clinical experts and an independent internal statistical expert.

11.9.2. Independent Data Monitoring Committee

An IDMC will be established to monitor unblinded data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. Members of the IDMC will be appointed by the study team. The IDMC will consist of at least 1 medical expert in the relevant therapeutic area(s) and at least 1 statistician. As required, the IDMC will make recommendations to the EC based on its ongoing review of study data. General details on the membership and responsibilities of the IDMC, and its communication with the EC will be provided in an IDMC charter, while technical details will appear in the SAP for this study.

11.9.3. Clinical Endpoint Committee

An independent blinded CEC will apply the protocol definitions and adjudicate and classify the following endpoints: symptomatic lower extremity DVT, symptomatic upper extremity DVT, non-fatal PE, asymptomatic proximal DVT of the lower extremity, incidental PE, VTE-related death, confirmed fatal/non-fatal ATE events, confirmed fatal/non-fatal VTE events, major bleeding, clinically relevant non-major bleeding events, and all-cause mortality. The independent blinded CEC will include leading scientific investigators with VTE, coagulation, diagnostics, and statistical expertise.

12. ADVERSE EVENT REPORTING

Refer to Section 9.2.1, Efficacy Evaluations and Outcomes, 9.2.2 Efficacy Endpoints, 9.3, Safety Evaluations, and Attachment 1, Reporting of Efficacy Endpoints, Adverse Events, and Serious Adverse Events for details on the AEs to be collected during this study.

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.

As of 15 September 2014, more than 84,000 subjects have been enrolled in interventional clinical trials (completed and ongoing Phase 1, Phase 2, Phase 3, and Phase 4) including more than 47,000 subjects treated with rivaroxaban and its overall safety profile has been well characterized. Appropriate information concerning AEs were systematically collected and submitted to regulatory authorities in the past. For the purposes of this study, certain nonserious

AEs will not be collected, while certain events will be collected as endpoints and therefore not reported as SAEs. All data on safety and efficacy outcomes will be reviewed regularly by an unblinded IDMC.

Section 12.2.1, Adverse Events Definitions and Classifications, describes the usual definitions of AEs and SAEs.

12.1. Warnings/Precautions

For rivaroxaban, Phase 1, 2, and 3 data are available (refer to Section 1, Introduction, and the IB) (Rivaroxaban IB 2014).[6] The known side effect profile for rivaroxaban can be found in the current IB. The IB is updated on a regular basis. Any new relevant information about side effects of rivaroxaban will be given to the subject and investigator.

In addition, the possibility of unforeseen side effects and allergic reactions to the drug, which can result in severe damage and even death, must always be considered.

12.2. Definitions

12.2.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE 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 Council 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 AEs starting with the signing of the ICF (refer to Section 12.4.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

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

For the purposes of this study, efficacy and safety outcomes will not be considered as AEs or SAEs (see Section 12.4.1 All Adverse Events).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For rivaroxaban, the expectedness of an AE will be determined by whether or not it is listed in the IB. For a non-sponsor investigational medicinal product (eg, a comparator product) with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.2.2, Attribution Definitions.

12.2.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE 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 AE 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 AE 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 AE 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).

12.2.3. Severity Criteria

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

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

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

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

Life-threatening: extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization or hospice care probable.

Death: the event results in death.

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

12.3. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor medicinal product, eg, name confusion)
- Exposure to a sponsor study drug from breast-feeding

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

12.4. Procedures

12.4.1. All Adverse Events

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

Suspected outcome events are excluded from AE/SAE collection and reporting, regardless of seriousness or severity. These suspected events will be captured on the eCRF as outcome events and will be waived from SAE collection and unblinding and exempted from expedited reporting. These events include:

- Symptomatic lower extremity proximal DVT
- Asymptomatic lower extremity proximal DVT
- Symptomatic lower extremity distal DVT
- Symptomatic upper extremity DVT
- Symptomatic non-fatal PE
- Incidental PE
- VTE-related death
- All-cause mortality
- ATE events (eg, MI, stroke)
- Visceral VTE
- All bleeding events

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

The following AEs or SAEs will be collected and entered into the eCRF, unless they are considered outcome events as specified in the list above. The SAEs need to be reported to the sponsor within the appropriate timeline as described in Section 12.2.1, Serious Adverse Events.

- Adverse events leading to permanent study drug discontinuation
- All SAEs that are not considered endpoint events as listed above

In addition, certain AEs are considered to be Adverse Events of Special Interest (AESI) and should be reported as SAEs. These include:

- Suspected severe hypersensitivity reaction (eg, anaphylaxis, angioedema, severe urticaria, bronchospasm)
- Severe skin reactions such as Stevens-Johnson Syndrome
- Suspected severe liver injury

All AEs and special reporting situations, as discussed in this section and in Section 12.3, Special Reporting Situations whether serious or nonserious, 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). Refer to Attachment 1, Reporting of Efficacy Endpoints, Adverse Events, and Serious Adverse Events for additional information on reporting of events in this study.

All outcome events will be monitored by the IDMC during the study and analyzed in the clinical study report after study termination. The IDMC will periodically review and assess all safety data for imbalances in safety endpoints. It is believed that in this way subject safety can continue to be monitored throughout the duration of the study, along with study integrity. If unexpected safety issues are identified, specific amendments will be implemented.

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

- Subject's name
- Subject number
- Subject's date of birth
- Study site number
- Investigator's name and 24-hour contact information
- Local sponsor's name and 24-hour contact information (for medical staff only)
- Statement, in the local language(s), that the subject is participating in a clinical study
- Any other information that is required to do an emergency breaking of the blind

12.4.2. Serious Adverse Events

All SAEs that are not outcome events as listed above occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

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

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes

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

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

- Hospitalization not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF)

12.4.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, and congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE 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.

12.5. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure

appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

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

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.4.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The study drug supplied for this study is rivaroxaban 10 mg and matching placebo, provided as round, white to yellow-white tablets, without markings. It will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

14.2. Packaging

The study drug, rivaroxaban and matching placebo will be packaged in bottles and will be 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 and the placebo, no storage restrictions (temperature, humidity, light) apply. The storage recommendation for rivaroxaban is room temperature (approximately 15°C 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 returned by study subjects will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

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 study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Central clinical laboratory manual
- Central clinical laboratory supplies
- IWRS manual
- Imaging materials

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

All subjects enrolled in this study will be scheduled to undergo systemic cancer therapy. This study will assess whether the administration of a novel, oral anticoagulant medication can safely be given for the primary prevention of VTE and provide important benefits to the subjects in the reduction of mortality or major morbid events. In accordance with the current NCCN and ASCO guidelines, the existing evidence base for optimal primary VTE prevention is in need of additional data from a robustly designed RCT such as this study. The specific form of thromboprophylaxis recommended for a given subject ultimately should be based on the treating physician's best clinical judgment.

It is unknown at the present time whether a direct, orally available inhibitor of FXa can or should be given for a prolonged period to prevent VTE primary events in cancer subjects. To minimize potential safety risks, subject safety will be closely monitored by the IDMC throughout the study. Given the extensive AE data currently available for rivaroxaban, a streamlined approach to collection of AE data is being utilized in this study, as described in Section 3.2, Study Design Rationale.

Women of childbearing potential who are enrolled in the study must agree to use an adequate birth control method or remain abstinent throughout the study, and pregnancy testing will be done on all women of childbearing potential before study entry and at the end of treatment.

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 AEs of the study, and provide their consent voluntarily will be enrolled.

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

The total blood volume to be collected is considered to be an acceptable volume for a subject with cancer.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials

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

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

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

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

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

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

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

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

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

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

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject 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 biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

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

Samples collected in this study may be stored for up to 5 years (or according to local regulations) for additional research and will not include molecular, biologic, or genetic studies. Samples will only be used to understand rivaroxaban, thromboprophylaxis in ambulatory cancer subjects, differential drug responders, and to develop tests/assays related to rivaroxaban. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.2.4, Withdrawal From the Study).

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 if the need for the product persists, 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 listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

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 study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

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

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and

date of study completion and reason for early discontinuation of the study drug or withdrawal from the study, if applicable.

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

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

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

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

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

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

17.5. Case Report Form Completion

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

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

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

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

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

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

17.6. Data Quality Assurance/Quality Control

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

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

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

17.7. Record Retention

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

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

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will

accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

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

17.8. Monitoring

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

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

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion

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

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

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

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

derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a clinical study report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory biomarker analyses performed after the clinical study report has been issued will be reported in a separate report and will not require a revision of the clinical study report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: Reporting of Efficacy Endpoints, Adverse Events, and Serious Adverse Events

Event category	Collected in the CRF (reviewed by IDMC)	Reported to Sponsor by Investigator (within 24 h)
Primary efficacy composite endpoint[a] including VTE/ATE related deaths	Yes (endpoint page)	No
Secondary efficacy endpoint[b] including all-cause mortality	Yes (endpoint page)	No
All bleeding events	Yes (endpoint page)	No
All other SAEs, and AESI	Yes	Yes
Nonserious AEs leading to permanent discontinuation from study drug treatment and AEs of particular concern to the investigator	Yes (AE page)	No
Other nonserious AEs	No	No
Pregnancy and pregnancy outcome	Yes (AE page)	Yes

AE=adverse event; AESI=adverse events of special interest; ATE=arterial thromboembolism; CRF=case report form; h=hour; IDMC=Independent Data Monitor Committee; SAE=serious adverse event; VTE=venous thromboembolism

[a] The primary efficacy composite endpoint is the composite of objectively confirmed symptomatic lower extremity proximal deep vein thrombosis (DVT), asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, or VTE-related death.

[b] The secondary efficacy endpoint includes: individual components of the primary efficacy composite variable, confirmed fatal/non-fatal ATE events, confirmed fatal/non-fatal visceral VTE events, composite of symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE, and all-cause mortality, and the composite of symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, and VTE-related deaths.

Attachment 2: Calculation of Creatinine Clearance

The CrCl (expressed as mL/min), is yielded by the Cockcroft and Gault formulas, relating serum creatinine, with age (in years) and body weight (in Kg).[a]

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

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

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

If creatinine concentration is measured in mg/dL, then the following 2 equations are used for men and women:

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

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

[a] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Attachment 3: Cancer-Associated Venous Thromboembolism Risk Score

A Modified Risk Stratification Model for Cancer-Associated Venous Thromboembolism

Patient Characteristic	Score
Cancer	
• Very high risk: stomach, pancreas[a]	2
• High risk: bladder, gynecologic, lymphoma, lung, renal[b] or testicular	1
Body mass index ≥35 kg/m^2	1
Platelet count ≥350,000/mm^3	1
Hemoglobin <10 g/dL	1
Leukocyte count >11,000/mm^3	1

[a] In the very high-risk category, primary brain tumors were removed since subjects with known brain tumors are excluded from study inclusion.

[b] Updated guidelines (inclusion of renal tumors): Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: Clinical Oncology Practice Guideline Update. J Clin Oncol 2013; 31:2189-2204.

Adapted from Sud R, Khorana AA. Cancer-associated thrombosis: risk factors, candidate biomarkers and a risk model. Thromb Res 2009;123(Suppl 4):S18-S21.

Attachment 4: Functional Status Assessment Tool

ECOG/WHO/Zubrod Performance Status Scale

0	Asymptomatic (fully active; able to carry on all predisease activities without restriction)
1	Symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; eg, light housework, office work)
2	Symptomatic, <50% in bed during the day (ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours)
3	Symptomatic, >50% in bed, but not bedbound (capable of only limited self-care; confined to bed or chair 50% or more of waking hours)
4	Bedbound (completely disabled; cannot carry on any self-care; totally confined to bed or chair)
5	Death

WHO=World Health Organization

Oken MM, Creech RH, Tormey DC, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Attachment 5: 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. During the baseline period, serum creatinine and several variables were measured in 1,628 subjects 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 in mg/dL:

GFR (mL/min1.73 m^2) = 186 x $(Pcr)^{-1.154}$ x $(age)^{-0.203}$ x (0.742 if female) x (1.210 if African American)

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

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 6: The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation for Estimating GFR

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$

where:

- S_{cr} is serum creatinine in mg/dL,
- κ is 0.7 for females and 0.9 for males,
- α is -0.329 for females and -0.411 for males,
- min indicates the minimum of S_{cr}/κ or 1, and
- max indicates the maximum of S_{cr}/κ or 1.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

INVESTIGATOR AGREEMENT

JNJ39039039/BAY59-7939 (Rivaroxaban)
Clinical Protocol BAY59-7939/39039039STM4001/18262 Amendment-4

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): Paul Burton, MD

Institution: [redacted]anssen Scientific Affairs

Signature: [redacted] Date: 20-FEB-2018
(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: 16 February 2018