Janssen Scientific Affairs *

Statistical Analysis Plan

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 STM4001; Phase [3b]

BAY59-7939/JNJ39039039STM4001 (Rivaroxaban)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

AMENDMENT HISTORY

All changes and clarifications of planned analyses in the SAP are listed below:

Topic or Section	Description of Changes and Clarifications of Planned Analyses
Changes from v5.0 to v6.0	
2.5 Definition of Study Dates	Imputation rule for partial exposure end dates was added to the rule of missing end dates.
Changes from v4.0 to v5.0	
2.5 Definition of Study Dates and Observation Period End Dates	Up-to-Day 180 observation period end date for subjects who withdrew early is maximum of withdrawal date and randomization date+180 days.
2.6 Subgroups	Subgroup criteria for the Khorana score is update to 2, 3, 4, and ≥5.
4.3 Treatment Compliance	Treatment compliance definition is updated. This is based on exposure data for subjects and based on the duration the subjects were in the trial.
4.5 Systemic Cancer Therapies and Concomitant Medications	Systemic cancer therapies taken at randomization and during the double-blind period as well as concomitant medications taken during double-blind period is defined.
5.2.4 Subgroup Analysis for Primary Efficacy Composite Endpoint	Subgroup analysis will be performed if there are at least 30 total randomized subjects in each subgroup category
5.6, 5.6.1 Additional Secondary Efficacy Variables Definition	A 3rd composite endpoint is added to the secondary efficacy endpoints. This is a composite of events in the primary efficacy composite endpoint, fatal/non-fatal ATE, and visceral VTE. A 4th composite endpoint is added to the secondary efficacy endpoints. This is a composite of symptomatic VTE events and major bleeding
9 Health Care Resource Utilization	Section heading relabeled and only descriptive statistics (frequency counts, mean, median, SD) will be presented.
Attachment	Added IDMC Data Preparation Specification.
Version 3.0 to 4.0	Document resaved with no changes made to v3.0
Changes from v2.0 to 3.0	
1.0 Introduction	Updated the version of the protocol to Amendment INT-4 finalized on February 16, 2018.
1.1 Study Objectives/Primary Objective	The occurrence of symptomatic lower extremity distal DVT event is included in the primary objective based on the amended protocol (v4.0).
1.3 Statistical Hypothesis for Study Objective	The occurrence of symptomatic lower extremity distal DVT event is included in the composite.
1.4 Sample Size Justification	Section updated based on the amended protocol (v 4.0). The following text is added – 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.
2.4 Definition of End-of-Study date	The End-of-Study date updated to include the last assessment date during the study, including the Day 210/Post-Treatment Follow-Up visit.
5.2 Primary Efficacy Composite Endpoint 5.2.1 Definition	The occurrence of symptomatic lower extremity distal DVT event is included in the primary efficacy composite endpoint.

5.2.4 Subgroup Analyses for the Primary Endpoint	Subgroup analysis will be performed if there are enough subjects in each subgroup (at least 5% of total randomized subjects). In addition, the Gail-Simon test is specified to assess interactions if found to be significant.
5.3 Competing Risk Analysis	The occurrence of symptomatic lower extremity distal DVT event is included in the primary efficacy composite endpoint for the analysis.
5.4 Key Secondary Endpoints	The occurrence of symptomatic lower extremity distal DVT event is included in the key secondary efficacy composite endpoint of symptomatic VTE events and VTE-related deaths
5.4.2 Analysis Methods	Additional supportive analysis of the key secondary endpoints based on the post-randomization observation period is included.
5.6 Additional Secondary Efficacy Endpoints	Definition of an ATE event is clarified. The occurrence of symptomatic lower extremity distal DVT event is included in the additional efficacy composite endpoint 1. Additional composite endpoint of symptomatic events and major bleeding event s added.
5.6.1 Definition	The time to first occurrence of fatal/non-fatal ATE is defined. Additional composite endpoint of symptomatic events and major bleeding event is added.
6.1.1 Bleeding Events Classification	Imputation rules for partial bleeding start dates is added.
Changes from v1.0 to v2.0	
1.2.1 Study Drug Discontinuation and Early Withdrawal from Double-Blind Period	Section added describing the details as per the protocol with regards to subject permanently discontinuing study drug.
2.3.1 Intent-to-Treat (ITT) Population 2.3.3 Per-Protocol (PP) Population	Section numbering corrected.
2.3.3 Safety Population	Section added with the definition of safety population.
2.4 Definition of Study Dates and Observation Period End Dates	Definitions of study dates and observation period end dates is further clarified.
2.5 Observation Periods	Table describing the efficacy and safety endpoints and analysis added.
2.5.1 Up-to-Day 180 Observation Period	Section renumbered to be 2.5.1. Censoring rule for subjects who did not experience an event during this observation period updated to be defined as censored at the last day of their complete assessment for study outcomes.
2.5.2 On-Treatment Observation Period	Imputation rule using a conservative approach for randomized subjects but never dosed is added.
2.5.3 Post-Randomization	Censoring rule for subjects who did not experience an event during this observation period updated to be defined as censored at the last contact date is clarified.
2.5.4 Post-First Dose Observation Period	Imputation rule using a conservative approach for randomized subjects but never dosed is added.
2.6 Definition of Subgroups	Tumor type subgroup is clarified.
4.3 Treatment Compliance	Imputation rule in the event of missing information on the returned number of tables added.
4.6 Study Discontinuation and Early Withdrawal from Double-Blind Period	Section updated to include two scenarios with regards to discontinuation from study treatment and withdrawal from double-blind period.

5.1.2 Data Handling Rules	Imputation rule for partial dates is added.
5.2.2 Analysis Methods	The primary composite endpoint analysis will be based on the Up-to-Day 180 observation period for the ITT population
5.2.2.1 Assessment of Proportional Hazards Assumption	In event of non-proportional hazards, alternative approaches were included.
5.2.3 Supportive Analyses for Primary Efficacy Composite Endpoint	Section updated to include supportive analysis based on the on-treatment observation period.
5.2.5.1 Additional Primary Efficacy Composite Endpoint – Include Distal DVT	Additional composite efficacy endpoint defined to include the occurrences of symptomatic lower extremity distal DVT and asymptomatic lower extremity distal DVT.
5.2.5.2 Sensitivity Analysis for Primary Efficacy Endpoint	Clarification for analysis is added.
5.3 Competing Risk Analysis	Section moved from 5.6.
5.4.2 Analysis Methods	Analysis of key secondary efficacy endpoints will be based on the up-to-day 180 observation period.
6.1.3 Supportive Analysis of the Primary Safety Endpoint of Bleeding	Additional supportive analysis of time to multiple bleeding event using recurrent event analysis is added.
Attachments	Illustrations with examples depicting the different observation periods including occurrences of events and censoring rules is added

ABBREVIATIONS

AE	adverse event
ATE	arterial thrombosis event
AESI	adverse event of special interest
APC	advanced pancreatic cancer
CEC	Clinical Endpoint Committee
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
eCRF	electronic case report form
CSR	Clinical Study Report
CU	compression ultrasonography
DPS	Data Presentation Specification
DVT	deep vein thrombosis
ECOG	European Cooperative Oncology Group
EODB	end-of-double-blind period
EOS	end-of-study
EOT	end-of-treatment
HR	Hazard ratio
IDMC	Independent Data Monitoring Committee
ISTH	International Society on Thrombosis & Haemostasis
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PE	pulmonary embolism
PK	pharmacokinetic(s)
PP	per-protocol
RRR	relative risk reduction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
T&E	Time and Events
TEAE	treatment-emergent adverse event
VTE	venous thromboembolism

1. INTRODUCTION

This statistical analysis plan (SAP) specifies definitions of analysis populations, derived variables, and statistical methods for analysis of efficacy and safety for the Phase 3b study BAY59-7939/JNJ39039039STM4001. This SAP is based on the Clinical Protocol BAY59-7939/JNJ39039039STM4001 Amendment INT-4 finalized on February 16, 2018.

Titles, mock-ups and programming instructions for all statistical outputs (tables, figures, and listings) will be provided in a separate document entitled Data Presentation Specifications (DPS). This study SAP will be finalized prior to database lock.

This study SAP is also used for the Independent Data Monitoring Committee (IDMC) pre-specified safety reviews. For the IDMC however the definitions and imputation rules are defined based on the data cutoffs and accumulating data at the time of each DMC meetings.

1.1. Study Objectives

Primary Objective

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 deaths 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 outcome variable, confirmed fatal/non-fatal arterial thromboembolism (ATE) events, confirmed fatal/non-fatal visceral 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 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.

1.2. Study Design

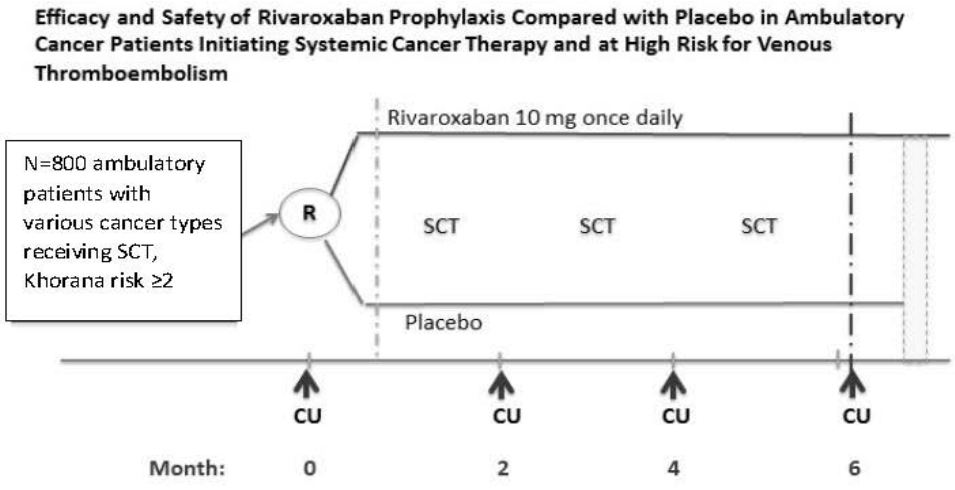
This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, superiority study comparing the efficacy and safety of rivaroxaban with placebo for primary prophylaxis of VTE (defined as DVT and/or PE) in ambulatory adult men and women, 18 years of age and older, with various cancer 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 (10 mg orally once daily for 180 days) or rivaroxaban (10 mg orally once daily for 180 days) for thrombo-prophylaxis based on their clinical status.

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 [for subjects who permanently stop study drug], 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.

A target of approximately 700 subjects will be randomly assigned into the study in a 1:1 ratio to 1 of 2 treatment groups (rivaroxaban 10 mg qd and placebo) with approximately 350 subjects per treatment group. Towards the end of the enrollment phase, the planned total of subjects to be randomized into the study was revised to approximately 800 subjects due to a higher than originally anticipated subject discontinuation rate. In addition, subjects will be stratified at randomization by tumor type (APC or non-APC) such that approximately 25% of the subjects randomly assigned are those with APC.

Randomized subjects will continue with their recommended systemic cancer therapy (SCT) during the study period and will be examined by compression ultrasonography (CU) at every 8-week intervals. Subjects permanently discontinuing the study drug will be required to have a CU performed within 2 days of receiving their last dose of study drug.

Figure 1: Schematic Overview of the Study



1.2.1. Study Drug Discontinuation and Early Withdrawal from Double-Blind Period

As per the protocol (Section 10.2.2), if a subject permanently discontinued study drug before the Day 180 visit/End of double-blind (EODB) period, this would not result in automatic permanent withdrawal of the subject from the study. Subjects are encouraged to make every effort to continue participation in the study and complete the schedule subsequent study visits until the planned end of their study double-blind duration (Day 180/EODB). All outcomes/events data (VTE, vital status (alive/dead), MI, stroke, and other thrombosis events) and safety data (including bleeding events) are collected. If a subject permanently discontinued study drug prior to Day 180 but continued in the study and completed all study visits up to Day 180, then this subject is considered as having 'completed the double-blind period' (that is, participated in the study up to the Day 180 visit).

All subjects including those who discontinued prior to Day 180 visit are contacted by telephone for a Day 210/EOS follow-up assessment. Any outcome/event data (including vital status) reported during this telephone visit is collected at this Day 210/EOS visit as agreed upon by the subject informed consent. In the event a subject withdrew consent or is lost-to-follow up, the vital status data are obtained through public information (death and other registries) per local guidelines and as allowed by local registration.

1.3. Statistical Hypotheses for Study Objectives

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, or VTE-related death in ambulatory adult subjects with various cancer types receiving systemic cancer therapy who are at high risk of developing a VTE.

1.4. Sample Size Justification

This is a 6-month fixed duration study to demonstrate the superiority of rivaroxaban compared with placebo in the ambulatory cancer subjects undergoing systemic cancer therapy. Sample size determination is provided in the protocol Section 11.2 and described below:

Estimates for VTE events in this population vary but point out to a significant benefit (or, reduction in events) over placebo when treated with anticoagulant therapy. Per a recent review of the VTE prophylaxis studies in cancer subjects by Khorana et al (protocol ref 20-22), most RCTs on solid tumors have reported relative risk reductions (RRRs) anywhere between 50% and 64%. The duration of the earlier primary prophylaxis studies 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, 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 $\geq$ 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 show a symptomatic VTE rate at 180 days of at least 12% in subjects with a Khorana thromboembolic risk score of >2 is reasonable. The adjudication of objectively confirmed asymptomatic DVT and PE is estimated to add an additional 5%-10 % to the primary efficacy composite endpoint.

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, our 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 six-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 fixed treatment duration of 6 months on each successfully randomized subject. Assuming a cumulative incidence rate of 14.5% for the primary 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% relative risk reduction (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 two 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)

1.5. Randomization and Blinding

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 (Advanced Pancreatic Cancer [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/End-of-Treatment) during the double-blind treatment period. The requestor must use his or her own user identification (ID) and personal identification number (PIN) 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.

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.

Pancreatic cancer subjects are at a higher risk to develop VTE (VTE Khorana risk score ≥2). These subjects are also more likely to discontinue early from the study. Therefore, higher than planned (25%) number of pancreatic subjects were allowed for enrollment into this study.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Data collected in the study from randomization through End-of-Double-Blind (EODB) will be re-assigned to visit windows based on the actual date of assessment (only for the ECOG performance status evaluation, laboratory and vital signs data).

The reference day is Study Day1 which will correspond to the randomization day. The relative day will be determined relative to Study Day 1.

The visit windows are based on the scheduled clinic visits (see Time & Events Schedule in protocol) and are defined below:

Period	Visit Window	Time Intervals[a] for Visit Window	Target Day[a] for Visit Window
Screening/Randomization	Baseline	≤1	1
Double-Blind Period	Week 8	>1 to 84	56
	Week 16	85 to 146	112
	Day 180/EODB[b]	≥147	180

[a] Based on actual study day of assessment; b = End of Double-Blind Period. No lab or vital signs data were collected at the Day 210 Follow-Up/End-of-Study visit

If more than one assessment falls in the same visit window, the one closest to the target date will be used in summary tables. In case of a tie (2 or more assessment which are equidistant), the latter assessment will be used.

2.2. Baseline

Baseline value is defined as the last observation prior to and including Day 1.

2.3. Pooling Algorithm for Analysis Centers

No pooling of centers (with varying number of randomized subjects) will be done.

2.4. Analysis Populations

2.4.1. Intent-to-Treat (ITT) Population

This analysis population consists of all randomized subjects.

2.4.2. Per-Protocol (PP) Population

This population is a subset of the ITT population. Subjects with predefined major protocol deviations will be excluded from the ITT population.

The predefined protocol deviations (based on major deviations) employed to define the PP population are:

- Randomized without informed consent (entered study but inclusion criterion #12 not met)
- Received wrong treatment (deviation recorded to be received wrong treatment or incorrect dose)
- Randomized but not treated
- Randomized but did not satisfy the key study entry criteria (inclusion criteria not met/exclusion criteria met)
    - Inclusion Criteria
        - #1 Ambulatory men and women ≥ 18 years of age
        - #4 Subject must have a Khorana thromboembolic risk score ≥2
    - Exclusion Criteria
        - #1 Subject has diagnosis of primary brain tumors
        - #2 Subject has known history of brain metastases
        - #3 Subject has bleeding diathesis, hemorrhagic lesions, active bleeding and other conditions with a high risk for bleeding
        - #4 Subject has hematologic malignancies with the exception of lymphoma
        - #8 Subject has evidence of VTE on screening Compression Ultrasound or incidental VTE identified on spiral computed tomography scans ordered primarily for staging or restaging of malignancy ≤30 days prior to randomization

All protocol deviations, including the deviations listed above will be examined and reviewed from a medical perspective prior to End-of-Study/database lock in a blinded fashion and subjects will be flagged accordingly in the final analysis database.

2.4.3. Safety Population:

This population is a subset of the ITT population, consisting of all randomized subjects who receive at least one dose of study drug.

2.5. Definition of Study Dates and Observation Period End Dates

The study dates and period end dates will be used to define the time period for data included in the analysis of efficacy and safety endpoints for the different observation periods (defined in Section 2.6).

Study Day 1 date: the date of randomization of the subject.

End-of-Study (EOS): the date of the last study-related procedure for the subject (EOS is defined as last assessment day during the study, including the Day 210/Post-Treatment Follow Up visit) and is defined as the minimum (last assessment day during the study, death date).

Double-Blind period start date will be the date of randomization.

Double-Blind period end date will be defined as the completion/early withdrawal date (date of completion or early withdrawal [any reason including death] from the double-blind period).

Up-to-Day 180 observation period end date will be defined as follows;

- Day 180/EODB completion date (for subjects who completed the double-blind period) or
- Death date (subjects who died during the double-blind period [DB reason=death] or during any time from randomization through Day 180 [died post withdrawal from DB but before Day 180/EODB visit) or
- Maximum (double-blind withdrawal date, randomization date + 180 days) for subjects who withdrew early from the double-blind period [any reason other than death] and had not died during the time from randomization through Day 180

First dose date: the date on which the first dose of study drug is taken by the subject. If missing or partial for a subject who takes study drug, the first dose date is set to the randomization date.

Last dose date: the date on which the last dose of study drug is taken by the subject (dose end date). If the dose end date is missing or partial for a subject who takes study drug, the last dose date is set as follows

- Maximum (Minimum (discontinuation date in the double-blind period [including death date during double-blind period], last visit date when drug is dispensed + number of pills dispensed - number of pills returned at following visit), imputed partial last dose date, exposure start date of last record))
    - Imputation rule for partial dates: If only the day is missing, then day imputed to the last day of that month. If day and month are missing, the date will be imputed to the start date if year is the same, else imputed to January 1st.

The last dose date will not be later than the double-blind period end date. The last dose date will not be before the first dose date and if a subject has not taken any study drug, the last study drug date will be set to missing.

2.6. Observation Periods

In this study, four observation periods will be defined. These are Up-to-Day 180, On-Treatment, Post-Randomization and Post-First Dose observation periods. An observation period refers to a time window. Analyses of primary and secondary efficacy as well as safety endpoints will include data within a specified observation period. The primary efficacy endpoint analysis will be performed for more than one observation period as shown in the table below.

Up-to-Day 180 observation period: Primary efficacy composite endpoint analyses (including supportive and sensitivity analyses described in Sections 5.2.3 and 5.2.5 respectively) and secondary efficacy endpoints analyses.

On-Treatment observation period: Primary efficacy composite endpoint supportive analysis. Primary and secondary safety analyses.

Post-Randomization and Post-First Dose observation periods: Primary efficacy composite endpoint supportive analyses.

<table>
<tr><th colspan="4">Analysis of Efficacy Endpoints (Refer to Sections 5.2, 0 for details)</th></tr>
<tr><th colspan="4">Analysis Population: ITT</th></tr>
<tr><th>Endpoint</th><th>Observation Period(s)</th><th>Endpoint</th><th>Observation Period</th></tr>
<tr><td>Primary Efficacy Composite Endpoint

Time 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</td><td>Primary
Up-to-Day 180

Sensitivity
Up-to-Day 180

Supportive
On-Treatment
Post-Randomization
Post-First Dose</td><td>Key Secondary Endpoints

1. Time to first occurrence of objectively confirmed symptomatic VTE events (symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, or symptomatic non-fatal PE) or VTE-related deaths
2. Time to all-cause mortality

Additional Secondary Endpoints</td><td>Key Secondary & Additional Secondary
Up-to-Day 180</td></tr>
<tr><th colspan="4">Safety Endpoints (Refer to Section 6.0 for details)</th></tr>
<tr><th colspan="4">Analysis Population: Safety</th></tr>
<tr><td>Primary Endpoint

Time to the first occurrence of objectively confirmed ISTH major bleeding event</td><td>Primary
On-Treatment</td><td>Secondary Safety Endpoints
On-Treatment

Time to first occurrence of:
1. Clinically relevant non-major bleeding
2. Minor bleeding
3. Composite bleeding (major, clinically non-major and minor)</td><td>Secondary
On-Treatment</td></tr>
</table>

2.6.1. Up-to-Day-180 Observation Period

This observation period includes data from randomization to Up-to-Day 180 end date (defined in Section 2.5).

Event: All efficacy events (with respect to deaths, *VTE-related deaths are counted as events for primary efficacy endpoint. For the secondary efficacy endpoints, all-cause deaths are counted as events*) that occurred from randomization through the Up-to-Day 180 end date (Section 2.5) will be included in the analysis of this observation period.

- Event time - The time to event is defined as the time from randomization to the time of the first event during this observation period.

Censoring: Subjects who did not experience an event during this observation period will be censored at the last day of their complete assessment for study outcomes.

Subjects who died during this observation period will be censored as of their death date for endpoint analyses not related to death.

- Censoring time - The time to censoring is defined as the time from randomization to the minimum of (last day of their complete assessment for study outcomes during the double-blind period [double-blind completion/withdrawal], death date [non VTE-related deaths for primary efficacy composite endpoint]).

2.6.2. On-Treatment Observation Period

This observation period includes data from the day of the **first dose of study drug to 2 days after the last dose of the study drug, inclusively** (dose dates defined in Section 2.5).

All randomized subjects will be included in the On-Treatment observation period. A conservative approach will be used for subjects who were randomized but never dosed to include any event that may occur even if the subject did not take study drug. This is defined to include VTE-related events that occur during the study even if the subject had not taken study drug. Only those events that occur prior to the double-blind period end date will be included in the on-treatment observation period.

Event: All efficacy and safety events (with respect to deaths, *VTE-related deaths are counted as events for primary efficacy composite endpoint. For Bleeding related deaths, major bleeding is counted as events for the primary safety endpoint*) that occurred from the date of first dose of study drug up to the last dose of study drug+2 days will be included in the analysis of the On-Treatment observation period.

- Event time - The time to event is defined as the time from first dose date to the time of the first event during this observation period.
    - For randomized subjects but never dosed: The time to event will be defined as the time from randomization to the time of the event during the time in study. This imputation rule will be applied only for the ITT population.

Censoring: Subjects who do not experience an event during this observation period will be censored.

Subjects who died during this observation period will be censored as of their death date for endpoint analysis not related to death.

- Censoring time - The time to censoring is defined as the time from first dose date to the minimum (earliest) of (last dose date+2 days, death date).
    - For randomized subjects but never dosed the time to censoring will be defined as the time from randomization to the minimum of (last day of their complete assessment for study outcomes during the double-blind period [double-blind completion/withdrawal], death date [non VTE-related deaths for primary efficacy composite endpoint]).

2.6.3. Post-Randomization Observation Period

This observation period includes all data from randomization to Day 210/EOS.

Specifically, this observation period will include all events that have occurred after randomization through Day 210/EOS inclusive of all events after completion of double-blind period/Day 180 through Day 210 as well as all events that occurred after subject had withdrew early from the double-blind period through Day 210.

Event: All efficacy events (with respect to deaths, *VTE-related deaths are counted as events for primary efficacy composite endpoint*) that occurred from the date of randomization up to the Day 210/End-of-Study [EOS] (defined in Section 2.5) will be included in the analysis of the Post-Randomization observation period.

- Event time - The time to event is defined as the time from randomization to the time of the first event during this observation period.

Censoring: Subjects who do not experience an event during this observation period will be censored.

Subjects who died during this observation period will be censored as of their death date for endpoint analysis not related to death.

- Censoring time - The time to censoring will be time from randomization to the minimum of (last contact date [up to and including the Day 210 = EOS date defined in Section 2.5], death date [non VTE-related deaths]).

2.6.4. Post-First Dose Observation Period

This observation period includes all data from the first dose of study drug to Day 210/EOS.

Specifically, this observation period will include all events that have occurred after first dose through Day 210 inclusive of all events after double-blind period completion/Day 180 through Day 210 as well as all events that occurred after subject had withdrew early from the double-blind period through Day 210.

All randomized subjects will be included and the imputation rule for event times for randomized subjects but never dosed described in Section 2.6.2 will also be applied for the analysis of data for this observation period. All events that occur prior to the End-of-Study date will be included in the post-first dose observation period.

Event: All efficacy events (with respect to deaths, *VTE-related deaths are counted as events for primary efficacy composite endpoint*) that occurred from the date of first dose up to the Day 210/End-of-Study[EOS] (Section 2.5) will be included in the analysis of the Post-First Dose observation period.

- Event time - The time to event is defined as the time from first dose date to the time of the first event during this observation period.
    - For randomized subjects but never dosed: The time to event will be defined as the time from randomization to the time of the event during the time in study. This imputation rule will be applied only for the ITT population.

Censoring: Subjects who do not experience an event during this observation period will be censored.

Subjects who died during this observation period will be censored as of their death date for endpoint analysis not related to death.

- Censoring time - The time to censoring is defined as the time from first dose date to the minimum (earliest) of (last contact date [up to and including Day 210 visit date = EOS date defined in Section 2.5], death date [non VTE-related deaths])
    - For randomized subjects but never dosed: The time to censoring will be defined as the time from randomization to the minimum of (last contact date [up to and including Day 210=EOS date, death date [non VTE-related deaths]).

Examples are illustrated in Figures in the Appendix.

2.7. Definition of Subgroups

Homogeneity of treatment safety and effects, both in hazard ratio (HR) and direction, will be assessed in the following subgroups classified at baseline:

- Stratification factor: Pancreatic (APC) or Non-Pancreatic (Non-APC)
- Age (18 - <65, 65- <75, ≥ 75 years)
- Sex (Male, Female)
- Race (White, Black, Asian, Other, Unknown, Not Reported)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown, Not Reported)
- BMI (<25, 25-<30, 30-<35, ≥35 kg/m^2)
- Tumor type (Gastric/GE Junction, Lung, Lymphoma, Ovarian, and Other [which will include all the remaining non-pancreatic cancer types])
- Stage of Disease (I, II, III, IV) based on the TNM classification
- Baseline Khorana Score (2, 3, 4, and ≥5)
- Baseline ECOG score (0-1, ≥ 2)
- Geographic region (North America, Western Europe, Eastern Europe)
    - North America (USA, Canada), Western Europe (Belgium, France, Germany, Italy, UK), Eastern Europe (Bulgaria, Czech Republic, Russia), South America (Brazil)
- Baseline Creatinine Clearance (30 to < 50, 50 to <80, ≥80 mL/min)

Race and ethnicity for subjects from France will be denoted as 'Not Reported' in the subgroup analysis as this information is not collected from France due to local regulations.

3. INTERIM ANALYSIS AND INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

No interim efficacy analysis is planned in this study and there are no pre-specified stopping rules planned in this study. However, an IDMC has been set up for this study to periodically assess the safety of subjects in this study and to evaluate the efficacy data as necessary to ensure that the safety of subjects is not compromised. Details of the IDMC roles, responsibilities, and key activities/timelines are provided in the IDMC charter.

The programming rules for deriving the analysis variables and the data tables for the IDMC meetings are specified in the data presentation specification document (DPS). Brief description is included in the Attachment.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Summaries of demographic and baseline characteristics, risk factors and medical history will also be provided by treatment group.

Descriptive statistics (such as mean, standard deviation, median, minimum and maximum) will be provided for continuous variables such as age (at baseline visit), weight, and height. Counts and (appropriate) percentages will be provided for categorical variables such as sex and race.

4.2. Disposition Information

The number of subjects included in the analysis populations (ITT, PP and safety) and number of subjects who completed or withdrew from the double-blind period will be summarized by treatment group and stratification factor: APC or non-APC.

Summaries of reasons for withdrawal from the double-blind period and permanent discontinuation of treatment will be provided by treatment group.

Time to study drug discontinuation will be summarized by treatment group using the Kaplan-Meier method.

Time to early study discontinuation will also be summarized by treatment group using the Kaplan-Meier method.

4.3. Treatment Compliance Based on Exposure

The following rules will be implemented to determine the compliance based on exposure information.

For subjects who died during the double-blind period and for those subjects who permanently discontinued their treatment early the compliance will be determined as:

Days on drug= [(last dose date-first dose date+1) – days of drug interruption]
Total exposure duration = last dose date-first dose date+1

Compliance (%) = [Days on drug/Total exposure duration]x100

For all other subjects who completed or withdrew (but had not ended treatment early) from double-blind period the compliance will be determined as:

Days on drug= [(last dose date-first dose date+1) – days of drug interruption]
Total exposure duration = double-blind end date-first dose date+1

Compliance (%) = [Days on drug/Total exposure duration]x100

4.4. Extent of Exposure

Duration of **double-blind treatment** is defined as the duration between the first dose date and last dose date, inclusive. Duration of treatment exposure will be summarized by treatment group.

Total treatment duration = last dose date - first dose date + 1.

The total number of temporary drug interruptions (>3 days) and reasons for interruptions will also be summarized by treatment group.

Duration of **double-blind period** will also be summarized. The duration of double-blind period is defined as the duration from randomization up to the double-blind period end date.

Duration of Double-Blind period = Double-blind period end date (completers or withdrew subjects) – randomization date + 1.

4.5. Systemic Cancer Therapies and Concomitant Medications

Systemic cancer therapies at randomization and during the double-blind period (those that started after randomization and those started before randomization by continued during the double-blind period) will be summarized by treatment group. The number and percentage of randomized subjects, who received systemic cancer therapies will be presented.

Concomitant medications include all medications received at or after the randomization date. These will be summarized by treatment group, for all randomized subjects, using the Anatomical Therapeutic Chemical (ATC) dictionary.

4.6. Study Drug Discontinuation and Early Withdrawal from Double-Blind Period

If a subject's study treatment must be permanently discontinued before the end of the double-blind treatment period, this will not result in automatic withdrawal of the subject from the study and they are encouraged to continue to be followed for efficacy and safety outcome until the end of the double-blind period/Day 180. Data from remaining scheduled visits are collected until the subject either completes the double-blind period/Day 180 visit or withdraws early from the study.

Outcome data for all subjects, those who completed the double-blind period as well as those who withdrew early from the double-blind period is also collected at the Day 210/EOS visit as agreed during the informed consent. Every effort will be made to follow-up the subject and collect the data including vital status. In the event a subject withdrew consent or is lost-to-follow up, the vital status data (dead/alive) will be obtained through public information (death and other registries) per local guidelines and as allowed by local registration.

Thus, there are two scenarios as described below:

1. Subject permanently discontinues study treatment but completes the double-blind period (i.e. completed the study/end of double-blind period)
    a. If subject experiences an efficacy (primary or secondary) endpoint event at any time during the study (from randomization through double-blind period completion), then the event and corresponding time to the occurrence of the event will be included in the analysis of primary efficacy composite endpoint
    b. If a subject has no efficacy composite endpoint event (primary or secondary) during the time in study, then this subject will be censored with the time to censoring defined as the time from randomization to last day of their complete assessment for study outcomes during the double-blind period [double-blind completion].
2. Subject permanently discontinues study treatment and withdraws early prior to the end of the double-blind period (i.e. withdrew from the study altogether) or dies during the double-blind period
    a. If subject experiences an efficacy composite endpoint event (primary or secondary, including VTE-related deaths) after withdrawing from the study and the time to the occurrence of the event is prior to Day 180, then this event and corresponding time to the occurrence of the event will be included in the analysis of primary efficacy composite endpoint. If subject dies (all causes other than VTE-related) after withdrawing from the study and reported on Day 210 but event time is prior to Day 180, then this event and corresponding time to death will be included in the all-cause mortality endpoint analysis
    b. If a subject does not experience any efficacy composite endpoint event (primary or secondary) in the study, then this subject will be censored. The time to censoring is defined as the time from randomization to the minimum of (last day of their complete assessment for study outcomes during the double-blind period/Day 180 [double-blind withdrawal date for those who withdrew], or death date [censored at death date for analysis not related to the specific death endpoint]).

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical tests will be 2-sided and conducted at 5% significance level unless specified otherwise.

The fixed-sequence step down procedure with a priori ordered hypotheses will be used to control the type I error for multiple testing (Section 5.5). If the result of a test in the sequence is not significant, the tests in lower hierarchical order will be interpreted as not significant regardless of the actual p-value. All confidence intervals will be estimated at the 95% level.

5.1.2. Data Handling Rules

The primary efficacy and key secondary endpoint analyses in this study will be based on the ITT analysis population (which includes all randomized subjects). All safety endpoints will be analyzed based on the safety analysis population (which includes all randomized subjects who receive at least one dose of study drug).

Time to event analyses will use censoring rules that apply to subjects with no primary efficacy outcomes during the specified observation periods, or, to subjects who withdrew from the study, or to subjects who die because of reasons other than VTE-related or bleeding, or withdrew informed consent before the end of the predefined treatment duration (Section 2.6 describes in detail all the censoring rules for the different observation periods).

All efforts will be made to collect complete data for all subjects randomized in this study to avoid missing or partial event dates. If the event date is not known, the investigators will provide their best estimate as to when the event occurred based on all the data available for that subject. In the extreme scenario where the event date is partial (missing day and month and year available), the day will be imputed as the first of the month.

5.2. Primary Efficacy Composite Endpoint

The primary efficacy outcome variables (objectively confirmed – CEC Adjudicated) that will be used to define the primary efficacy composite endpoint are:

- 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

5.2.1. Definition

The primary efficacy composite endpoint is defined as the time 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 as adjudicated by the independent Clinical Endpoint Committee (CEC).

5.2.2. Analysis Methods

The primary efficacy composite endpoint analysis will be based on the **'Up-to-Day 180' observation period for the ITT population** with censoring as defined in Section 2.6.

The cumulative distribution function of the time to first occurrence of the primary efficacy composite endpoint will be estimated by the Kaplan-Meier method. The primary statistical hypothesis will be tested using a log-rank test, stratified by tumor type (APC or non-APC).

The estimate of the hazard ratio (HR), RRR (RRR=100*[1-HR] %) and the 95% confidence intervals for the treatment effect will be provided based on a stratified Cox proportional hazard model (stratification factor: APC or non-APC) and including treatment group as a binary covariate (i.e., rivaroxaban, placebo).

The cumulative event rate derived from Kaplan-Meier estimate will also be displayed graphically to evaluate the timing of event occurrence and the consistency of the treatment effect over time.

5.2.2.1. Assessment of Proportional Hazards Assumption

The proportional hazards assumption in the primary efficacy time-to-event endpoint analysis based on the Cox-proportional hazard model will be assessed graphically using

- -log(-log) plots
- The goodness of fit testing approach as proposed by Harrell and Lee (1986)[1,2], a variation of a test originally proposed by Schoenfeld (1982)[3]
  (Kleinbaum and Klein (2012)[4] provide details on the implementation of this approach).

In the event of non-proportional hazards, alternative approaches will be used that include the Peto-Prentice test (Peto and Peto, 1972[5]; Prentice, 1978[6]) and Fleming-Harrington (1984[7]) test (with parameters for this test defined at p=1 and q=0). All tests will be performed with the use of SAS version 9.4 or higher (SAS Institute). Additional data explorations will be carried out to assess the non-proportionality of hazards between groups.

5.2.3. Supportive Analyses for Primary Efficacy Composite Endpoint

To assess the robustness of the conclusion of the primary analysis, supporting analyses of the primary efficacy composite endpoint will be performed based on different observation periods and analysis populations as described below with censoring rules defined in Section 2.6:

- Based on the **'On-Treatment' observation period** for the ITT population
- Based on the **'Up-to-Day 180' observation period** for the PP population
- Based on the **'On-Treatment' observation period** for the PP population
- Based on the **'Post-Randomization' observation period** for the ITT population
- Based on the **'Post-First Dose'** observation period for the ITT population

In all cases, the 2-sided 95% confidence interval (CI) for the hazard ratio (rivaroxaban vs placebo) will be provided using the stratified Cox proportional hazards model (stratification factor: APC or non-APC) and including treatment group as a binary covariate (i.e., rivaroxaban, placebo).

The cumulative event rate derived from Kaplan-Meier estimate will also be displayed graphically to evaluate the timing of event occurrence and the consistency of the treatment effect over time and tested using a log-rank test, stratified by tumor type (APC or non-APC).

Summary of Primary Efficacy Composite Endpoint Analysis Methods			
Endpoint	**Observation Period**	**Analysis Population**	**Method**
Primary Efficacy Composite Endpoint (CEC Adjudicated Events)	**Primary** Up-to-Day 180	ITT	<u>Primary Analysis</u> Kaplan-Meier Estimates (Cumulative event rates and stratified log-rank test) Cox-model (HR, 95% CI)
	Supportive On-Treatment	ITT	
	Up-to-Day 180	PP	
	On-Treatment	PP	
	Post-Randomization	ITT	
	Post-First Dose	ITT	
	Up-to-Day 180	ITT	<u>Sensitivity Analysis</u> 1. Include asymptomatic distal DVT 2. Dropout with no follow up – treating time to discontinuation as being time to an event.
	Up-to-Day 180	ITT	<u>Competing Risk Analysis</u> Deaths due to causes other than VTE-related will be a competing risk event Gray's 2-sampel test (Cumulative Incidence Function) Fine and Gray regression model

5.2.4. Subgroup Analyses for the Primary Efficacy Composite Endpoint

Analyses of the primary efficacy composite endpoint will also be performed to examine the consistency of treatment effect across subgroups listed in Section 2.7. Homogeneity of treatment effect will be evaluated using the same model as described in Section 5.2.2 (stratified Cox proportional hazard model with treatment as a covariate). Subgroup analysis will be performed if there are at least 30 total randomized subjects in each subgroup category. Only descriptive

summaries will be presented for subgroups with fewer subjects. *The subgroup analysis by race and ethnicity will be denoted as 'Not Reported' for subjects from France as this information is not collected from the sites due to local regulation.*

The interaction of treatment with each of the subgroups will be analyzed based a stratified Cox proportional hazard model with stratification factor and treatment group with additional terms for subgroup and subgroup-by-treatment interaction. Further evaluations will be performed to assess and explain the nature of the interaction (qualitative or quantitative) if a significant (p value <0.10) interaction is observed. Significant interactions will be examined using a two-sided Gail-Simon[8] test. Descriptive statistics (n, mean, standard deviation, median, and range) will be presented by treatment groups for each subgroup.

The subgroup analyses of the primary efficacy composite endpoint will be based on the **'Up-to-Day 180'** observation period for the ITT population with censoring as defined in Section 2.6.

5.2.5. Sensitivity Analyses

5.2.5.1. Additional Primary Efficacy Composite Endpoint – Include Asymptomatic Distal DVT

An additional composite efficacy endpoint will also be defined to *include the occurrences of 'asymptomatic lower extremity distal DVT'*.

Sensitivity analysis will be performed on the time to the first occurrence of objectively confirmed symptomatic lower extremity proximal DVT, asymptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, asymptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, incidental PE or VTE-related death as adjudicated by the independent Clinical Endpoint Committee (CEC). This analysis will be based on the ITT analysis population for the **'Up-to-Day 180'** observation period.

Cumulative distribution function of the time to first occurrence will be estimated by the Kaplan-Meier method and tested using a log-rank test, stratified by tumor type (APC or non-APC).

The estimate of the hazard ratio (HR), RRR (RRR=100*[1-HR] %) and the 95% confidence intervals for the treatment effect will be provided based on a stratified Cox proportional hazard model (stratification factor: APC or non-APC) and including treatment group as a binary covariate (i.e., rivaroxaban, placebo).

5.2.5.2. Sensitivity Analysis for Primary Efficacy Composite Endpoint

In this study, all data regarding occurrence of DVT, PE events and vital status (alive/dead) events will be collected for all subjects (completers and early withdrawal) at the Day 210/follow-up visit. Data for the primary efficacy composite endpoint will be missing for subjects for whom the Day 210/follow-up visit is not performed or if the visit was performed but the occurrence of an event was reported as unknown. A conservative approach will be used for subjects who withdrew from the double-blind period and did not have an event during the double-blind period.

In this approach, subjects who withdrew from the double-blind period for any reason other than death and were censored (i.e. had not experienced any VTE-related primary efficacy event during the double-blind period) and have missing or unknown Day210/follow up status will be considered as having a VTE-related event (i.e. not censored). The time from randomization to time of withdrawal will be assumed to be the time to an occurrence of a VTE-related primary efficacy composite event (no specific individual component will be assigned as the worst case).

The sensitivity analysis for the primary efficacy composite endpoint will be based on the **'Up-to-Day 180'** observation period for the ITT analysis population. For the above sensitivity analyses, the cumulative distribution function of the time to first occurrence will be estimated by the Kaplan-Meier method and tested using a log-rank test, stratified by tumor type (APC or non-APC).

The estimate of the hazard ratio (HR), RRR (RRR=100*[1-HR] %) and the 95% confidence intervals for the treatment effect will be provided based on a stratified Cox proportional hazard model (stratification factor: APC or non-APC) and including treatment group as a binary covariate (i.e., rivaroxaban, placebo).

5.3. Competing Risk Analysis

Competing risks arise when subjects are at risk of experiencing more than one cause of failure (event) and failure due to other causes precludes observing the main cause of interest (i.e. censored for primary efficacy composite endpoint).

The primary efficacy composite endpoint is defined as a composite 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 (adjudicated by CEC). For this type of outcome (the primary endpoint), a death due to causes other than VTE-related is a competing risk event and, as such, a patient is no longer at risk of having any of the events of interest.

To account for competing risks (deaths from causes other than venous thromboembolism related; VTE-related deaths are included in the primary efficacy composite endpoint) in the primary efficacy analysis, a cumulative incidence approach will be followed with the use of Gray's (1988)[9] two-sample test (two-sided alpha level, 0.05). Hazard ratios and 95% confidence intervals will be calculated with the use of the Fine and Gray (1999)[10] regression model (with treatment group as a factor). Cumulative incidence functions (defined as the cumulative probability of failure from a specific cause over time) will be estimated separately for the two study groups. These analyses will be based on the **'Up-to-Day 180'** observation period for the ITT population with censoring as defined above in Section 2.6.

5.4. Key Secondary Endpoints

The key secondary efficacy outcomes (objectively confirmed – CEC Adjudicated) are:

- symptomatic VTE events (symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT and symptomatic non-fatal PE) or VTE-related deaths
- All-cause mortality

5.4.1. Definition

The key secondary efficacy endpoints defined based on the key secondary efficacy outcomes above are as follows:

- Time to first occurrence of objectively confirmed symptomatic VTE events (symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, or symptomatic non-fatal PE) and VTE-related deaths
- Time to all-cause mortality

5.4.2. Analysis Methods

Analysis of the key secondary efficacy endpoints will follow the same approach as in the analysis of the primary efficacy composite endpoint analysis. The analysis will be based on the **'Up-to-Day 180'** observation period for ITT population with censoring as defined above (Section 2.6). Each of the key secondary endpoints will be tested using a log-rank test, stratified by tumor type.

For each of these two key secondary endpoint analyses, a Cox proportional hazard model with treatment and stratification factor as covariates will be fitted. A point estimate along with 2-sided 95% CI for the treatment effect of RRR (RRR=100 x [1-HR] %) will be provided.

The cumulative event rate derived from Kaplan-Meier estimate will also be displayed graphically to evaluate the timing of event occurrence and the consistency of the treatment effect over time.

Summary of Key Secondary Efficacy Endpoints Analysis Methods

Endpoint	Observation Period	Analysis Population	Method
Key Secondary Endpoints 1. Composite of symptomatic VTE events or VTE-related death 2. All-cause mortality (CEC Adjudicated Events)	Up-to-Day 180	ITT	Kaplan-Meier Estimates (Cumulative event rates and stratified log-rank test) Cox-model (HR, 95% CI)

5.5. Adjustment for Multiplicity

Superiority of rivaroxaban over placebo on the primary efficacy composite endpoint will be first established. If this is established, then a sequential approach using a closed testing hierarchical procedure (to control the family-wise type I error rate at alpha at 5%, 2-sided) will be used to test the following two secondary hypotheses:

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

Overall Hierarchy of Testing Multiple Hypothesis	
Primary Efficacy Composite Endpoint (ITT/Up-to-Day 180)	
• Time to first occurrence 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 or VTE-related death	α=0.05
↓	
Secondary Efficacy Endpoints (ITT/Up-to-Day 180)	
• Time to first occurrence of symptomatic VTE events and VTE-related death	α=0.05
↓	
• All-cause mortality	α=0.05

5.6. Additional Secondary Efficacy Variable(s)

Additional secondary outcomes (objectively confirmed – CEC Adjudicated) are:

- Individual components of the primary efficacy composite variable
- Confirmed fatal/non-fatal arterial thrombosis event (ATE) (e.g. MI and stroke) events (these will include the following events: occurrence of a stroke, MI or any arterial thrombosis event)
- 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
- Composite of events in the primary efficacy composite endpoint, fatal/non-fatal ATE, visceral VTE
- Composite of symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE and VTE-related deaths and major bleeding events

5.6.1. Definition

Secondary efficacy endpoints defined based on the other secondary outcomes above are as follows:

- Individual components of the primary efficacy composite variable
    - Time to first occurrence of symptomatic lower extremity proximal DVT
    - Time to first occurrence of asymptomatic lower extremity proximal DVT
    - Time to first occurrence of symptomatic lower extremity distal DVT
    - Time to first occurrence of symptomatic upper extremity DVT
    - Time to first occurrence of symptomatic non-fatal PE
    - Time to first occurrence of incidental PE
    - Time to VTE-related death

In addition to the analysis of the individual components, concordance between the investigator reported events and the CEC adjudicated events will also be presented.

- Time to first occurrence of fatal/non-fatal ATE (a composite of occurrence of MI, stroke [ischemic infarction with or without hemorrhagic conversion or primary hemorrhagic events – intraparenchymal hemorrhage, subdural hematoma or epidural hematoma] or any other ATE recorded on eCRF) event.
- Time to first occurrence of fatal/non-fatal visceral VTE event (include only visceral (venous) events recorded on the eCRF).
- Composite endpoint #1: Time to first occurrence of the composite endpoint 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: primary efficacy composite endpoint event components but including all-cause mortality*).
- Composite endpoint #2: Time to first occurrence of 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 (*composite: symptomatic events only and VTE-related deaths*).
- Composite endpoint #3: Time to first occurrence of the primary efficacy composite endpoint (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 deaths), fatal/non-fatal ATE (composite of MI, stroke or any ATE), and fatal/non-fatal visceral VTE event (*composite: primary efficacy composite endpoint event components, ATE events, and visceral VTE events*).
- Composite endpoint #4: Time to first occurrence of the composite of symptomatic lower extremity proximal DVT, symptomatic lower extremity distal DVT, symptomatic upper extremity DVT, symptomatic non-fatal PE, VTE-related deaths, and major bleeding event (*composite: symptomatic events and include major bleeding events for the ITT population and up-to-Day 180 observation period*).

5.6.2. Analysis Methods

Analysis of the other secondary efficacy endpoints will follow the same approach as in the analysis of the primary efficacy endpoint analysis. These analyses will be based on the **'Up-to-Day 180'** observation period for the ITT population with censoring as defined above (Section 2.6).

In addition to be above endpoints, the key secondary endpoints (time to symptomatic VTE events or VTE-related deaths, all-cause mortality) will also be analyzed based on the **'Up-to-Day 180'** observation period for the ITT population.

The cumulative distribution function of the time to first occurrence of each of these endpoints will be estimated by the Kaplan-Meier method and tested using a log-rank test, stratified by tumor type. In addition, a Cox proportional hazard model with treatment and stratification factor as covariates will be fitted. A point estimate along with 2-sided 95% CI for the treatment effect of RRR (RRR=100 x [1-HR] %) will be provided.

The cumulative event rate derived from Kaplan-Meier estimate will also be displayed graphically to evaluate the timing of event occurrence and the consistency of the treatment effect over time. No multiplicity adjustment will be performed for the analysis of these endpoints.

Frequency summary (N, %) of the total number of deaths and the primary cause of death, total number of subjects with myocardial infarction (MI), stroke, and other arterial thrombosis (ATE) events will also be presented for the Up-to-Day 180 observation period.

5.7. End-of-Study Vital Status Summary

In this study, vital status data (alive/dead) was collected at the Day 210 follow up visit for all randomized subjects, except for those who had died during the double-blind period. The Cochran-Mantel-Haenszel (CMH) test, adjusting for the stratification factor (APC/non-APC), for the association between the treatment group and each of these endpoints will be performed provided there are non-zero entries in each cell of the 2x2 treatment-by-endpoint table.

6. SAFETY

6.1. Bleeding

The primary safety objective of this study is to assess the major bleeding events as defined by International Society on Thrombosis and Haemostatis (ISTH) based on the CEC classification from the time of first dose to two days after the last dose of study drug.

6.1.1. Bleeding Events Classification

Like efficacy outcomes, the same independent CEC will adjudicate and classify bleeding events per the definitions in the CEC Charter.

Bleeding events will be classified as major, clinically relevant non-major, or minor bleeding using the ISTH classification 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 red blood cells or whole blood, or
- Occurrence at a critical site defined as intracranial, intra-spinal, intraocular, pericardial, intra-articular, intra-muscular with compartment syndrome, retroperitoneal, or
- Fatal outcome

Clinically Relevant Non-Major Bleeding

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

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

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 (corresponds to minimal bleeding event captured on the case record form).

Imputation Rules for Partial Bleeding Start Dates

If the bleeding start date is a partial date (only unknown day)

- If only the day is missing, and the month and year are known, the month and year of the AE will be compared with the month and year of double-blind medication start date.
    - If the both the month and year of the bleeding event is equal to the month and year of double-blind medication start date, then the imputed day will be the start day of medication.
    - If the month or the year of the bleeding event is different, then the imputed day will be the 1st day of the month.

6.1.2. Primary Safety Endpoint of Bleeding

The primary safety endpoint is ISTH major bleeding as adjudicated by the CEC.

6.1.2.1. Definition

The primary safety endpoint is defined as the time from the first study drug to first occurrence of ISTH major bleeding events in Section 6.1.1 during the **'On-Treatment'** observation period (observation periods defined in Section 2.6).

Censoring - subjects who do not experience endpoint events during the **'On-Treatment'** observation period will be censored at the minimum of (last dose date + 2, death date).

6.1.2.2. Analysis Methods

The primary safety endpoint will be analyzed using the same approach as in the primary efficacy endpoint but based on the **'On-Treatment'** observation period for the Safety population (randomized and taken at least one dose of the study drug) with censoring as defined above.

The cumulative distribution function of the time to first occurrence of the primary safety endpoint will be estimated by the Kaplan-Meier method and tested using a log-rank test, stratified by tumor type.

The estimate of the hazard ratio (HR), RRR (RRR=100*[1-HR] %) and the 95% confidence intervals for the treatment effect will be provided based on a stratified Cox proportional hazard model (stratification factor: APC or non-APC) and including treatment group as a binary covariate (i.e., rivaroxaban, placebo).

Incidence of major bleeding events and primary location of bleeding will also be summarized for each treatment group.

The primary safety endpoint will also be summarized for the subgroups defined in Section 2.7.

6.1.3. Supportive Analysis of the Primary Safety Endpoint of Bleeding

In addition to the primary safety analysis for major bleeding safety endpoint, supportive analysis will be performed to account for multiple major bleeding event times experienced by the same subject. Multiple major bleeding events will be analyzed using the recurrent event analysis by Anderson-Gill (1982)[11] method. The supportive analyses will be performed for the ISTH major bleeding endpoint and the clinically relevant non-major bleeding endpoint and will be based on the **'On-Treatment'** observation period for the safety analysis population. All tests will be performed with the use of SAS version 9.4 or higher (SAS® Institute).

6.1.4. Secondary Safety Endpoints of Bleeding

6.1.4.1. Definition

Secondary safety endpoints of bleeding include time to:

- Clinically relevant non-major bleeding
- Minor bleeding (corresponds to minimal bleeding)
- Any bleeding event (defined as a composite of ISTH major, clinically relevant non-major and minor bleeding)

6.1.4.2. Analysis Methods

The secondary safety endpoints of bleeding will be analyzed using the same approach as in the primary safety endpoint. The analysis will be based on the Safety population in the **'On-Treatment'** observation period with censoring as defined above (Section 2.6).

Each of the secondary endpoints will be tested using a log-rank test, stratified by tumor type (APC or non-APC). In addition, a Cox proportional hazard model with treatment and stratification factor as covariates will be fitted. A point estimate for hazard ratio (rivaroxaban/placebo) along with 2-sided 95% CI for the treatment effect of RRR (RRR=100 x [1-HR] %) will be provided.

The cumulative event rate derived from Kaplan-Meier estimate will also be displayed graphically to evaluate the timing of event occurrence and the consistency of the treatment effect over time.

Summary of Safety Endpoints Analysis Methods

Endpoint	Observation Period	Analysis Population	Method
Primary Endpoint ISTH Major bleeding event **Secondary Endpoints** 1. Clinically relevant non-major bleeding 2. Minor bleeding 3.Composite bleeding event (major, clinically non-major and minor) (CEC Adjudicated Events)	On-Treatment	Safety	Kaplan-Meier Estimates (Cumulative event rates and log-rank test) Cox-model (HR, 95% CI)

6.2. Adverse Events

The original terms used in the CRFs by investigators to identify AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher.

A treatment-emergent adverse event (**TEAE**) is defined as any adverse event that starts between the first study medication administration and the last study medication administration + 2 days.

Only the AEs with start dates between the first dose date and the last dose date+2 days will be included in all TEAE summaries, including study (double-blind period) withdrawal and treatment discontinuation.

As per the protocol (Section 12.4), in this study 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 (e.g., MI, stroke), visceral VTE, and all bleeding events.

The number (%) of subjects who had treatment-emergent adverse events will be summarized by System Organ Class (SOC) and preferred term (PT) for the Safety analysis population.

The number and percentage of subjects experiencing TEAEs will be summarized by treatment group for the Safety analysis population, and stratification factor: APC or non-APC.

In addition, overall summaries of **all AEs** (all AEs that are reported from start of study through the Day 210/End-of-Study) for the safety population will also be presented. Summary table of AE by body system and preferred term will also be presented for all AEs.

Adverse events will also be summarized by treatment group, severity, relationship to study medication, combined severity and relationship to study medication, action taken during treatment, and subject outcome. They will also be presented by treatment group, SOC, and PT.

Differences in the percentages of AEs between the two groups will be summarized and the 95% CI for the difference using the normal approximation to binomial distribution will be provided.

6.2.1. Imputation Rules for Missing AE Dates

A conservative approach will be used to handle the missing dates for adverse events. The rules for handling the incomplete AE onset dates will be as follows:

- If only the day is missing, and the month and year are known, the month and year of the AE will be compared with the month and year of double-blind medication start date.
    - If the both the month and year of the AE is equal to the month and year of double-blind medication start date, then the imputed day will be the start day of medication.
    - If the month or the year of the AE are different, then the imputed day will be the 1st day of the month.
- If only the month is missing, and day and year are known, the year of the AE will be compared with the year of the double-blind medication start date.
    - If the year of the AE is equal to the year of the double-blind medication start date, then the imputed month will be the same as the month of the double-blind medication.
    - If the year is different, then the month will be as January.
- If both the day and month are missing but year is known, compare the year with the year of the double-blind medication start date.
    - If the year is the same, then impute the AE start date as the same as the first dose date.
    - If the year is different, then impute the AE start date to be January 1.
- If the day, month and year are all missing, then the imputed date for the AE will be the date of the first dose of study medication.

After imputation if the AE start date is greater than the AE end date, then the AE start date will be set equal to the AE end date.

- No imputation will be done for AE end date.

6.2.2. Adverse Events Resulting in Withdrawal from the Study and Discontinuation of Treatment:

The number and percentage of subjects who withdrew from the double-blind period due to an **TEAE** (TEAE led to withdrawal from the study) will be summarized by treatment group and listed by subject. In addition, **TEAEs** that led to discontinuation of study drug (drug withdrawal) will also be summarized by treatment group.

In addition, overall summaries of **all AEs** (all AEs that are reported from start of study through the Day 210/End-of-Study) with action taken of drug withdrawal will also be presented

6.2.3. Serious Adverse Events (SAE) and Deaths during the Study:

The number and percentage of serious TEAE and deaths will be summarized by treatment group and listed by subject.

Serious TEAE that led to study drug discontinuation will be summarized by treatment group and listed by subject.

In addition, **all serious AEs** and deaths (all AEs that are reported from start of study through the Day 210/End-of-Study) will also be summarized.

6.2.4. Adverse Events of Special Interest

In addition to the overall AEs summaries, certain AEs that are considered to be Adverse Events of Special Interest (AESI) will be summarized. The special interest TEAEs for the following groups will be summarized:

- Suspected severe hypersensitivity reaction
  - SMQ preferred terms included are: anaphylaxis, angioedema, severe urticaria, bronchospasm, idiopathic urticaria, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactic shock.
- Severe skin reactions
  - SMQ preferred terms included are: Stevens-Johnson Syndrome.
- Suspected severe liver injury
  - SMQ preferred terms included are: drug-induced liver injury, acute hepatic failure, hepatic failure, hepatocellular injury, liver injury, mixed liver injury, alanine aminotransferase abnormal, alanine aminotransferase increase, aspartate aminotransferase abnormal, aspartate aminotransferase increased, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinaemia, and liver function test abnormal.

Summaries of the special interest TEAEs will be based on the safety population.

6.3. Clinical Laboratory Tests

Descriptive statistics for each clinical laboratory analyte (collected at baseline and at Week 8, Week 16, and EODB will be provided. Changes from baseline at each post-baseline visit will be calculated by treatment group and will be based on the safety population in the **'Up-to-Day 180'** observation period. The number of shifts from baseline in the categories of test results (low, normal, high) will be summarized by treatment group. A clinical laboratory test value is considered abnormal if it is outside the reference range (provided by the laboratory). Incidences of abnormal laboratory values will be summarized by treatment group based on subjects who have non-missing baseline and non-missing post-baseline values.

All laboratory test summaries will be based on the safety population (data from first dose through Day 180). Laboratory data from the central lab Covance will only be included in the summaries.

6.4. Vital Signs and Physical Examination Findings

Vital Signs

Descriptive statistics (mean, median, standard deviation, range, and number of observations) for blood pressure (systolic and diastolic) and pulse will be provided by treatment group for the safety analysis population. The changes from baseline for vital signs will also be summarized by treatment group at each visit.

Physical Examinations

Listings of physical examination results will be provided.

All vital signs and physical examination summaries will be based on the safety population (data from first dose through Day 210).

6.5. Electrocardiogram

N/A

6.6. Other Safety Parameters

N/A

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Pharmacokinetics samples collected at Month 2 (Week 8) will be analyzed and descriptive statistics (n, mean, standard deviation, median, and rage) for plasma concentrations will be provided.

7.2. Pharmacodynamics

N/A

8. BIOMARKER

In this study, biomarker samples are collected at screening, month 2 (Week 8), month 4 (Week 16) and month 6 (EODB). Biomarker assessments which include D-dimer, soluble P-selectin, and Tissue Factor (Factor III) will be summarized as part of the laboratory data summary.

9. HEALTH CARE RESOURCE UTILIZATION

The Health Care Resource Utilization (HCRU) data will be collected as part of the endpoint assessments for all patients. The HCRU data will be specific to the study outcomes of DVT, PE, or bleeding, including outpatient visits to health care providers (including all specialties), hospitalizations (including admittance to intensive care unit), time to first hospitalization (DVT, PE, bleeding or an AE), length of hospitalization (defined as the sum of the duration of days over all the hospitalizations), and use of diagnostic procedures (type of imaging or diagnostic tests performed). Descriptive summaries (frequency counts and mean, median, SD) will be provided for the HCRU. All summaries will be presented by treatment group for the ITT analysis population.

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ATTACHMENT: EXAMPLES OBSERVATION PERIOD AND EVENT/CENSORING TIME

The different observation periods and the time intervals within which study data will be included are shown in the figures below.

Figure 1: Up-to-Day 180 observation period

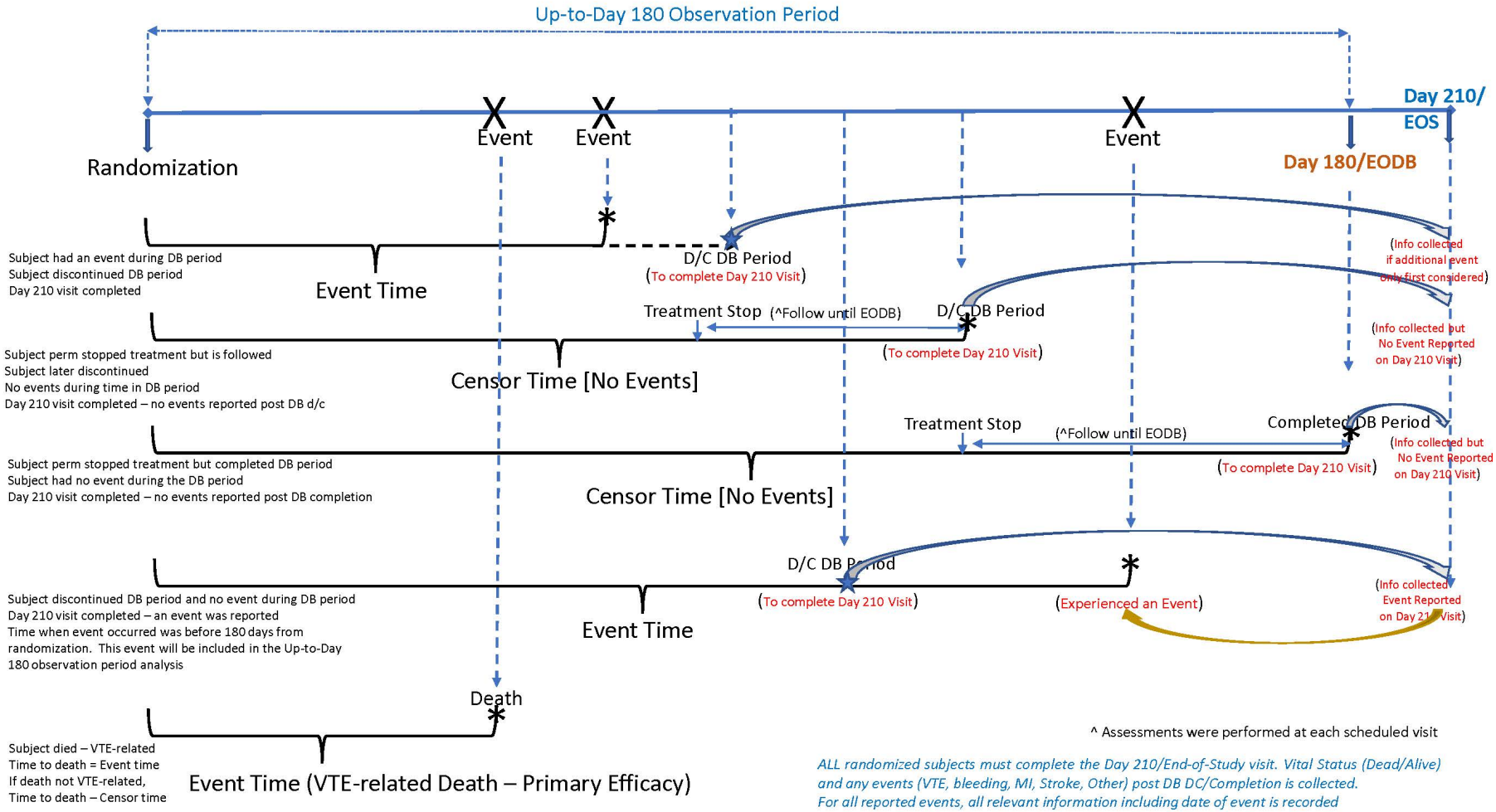


Figure 2: On-Treatment observation period

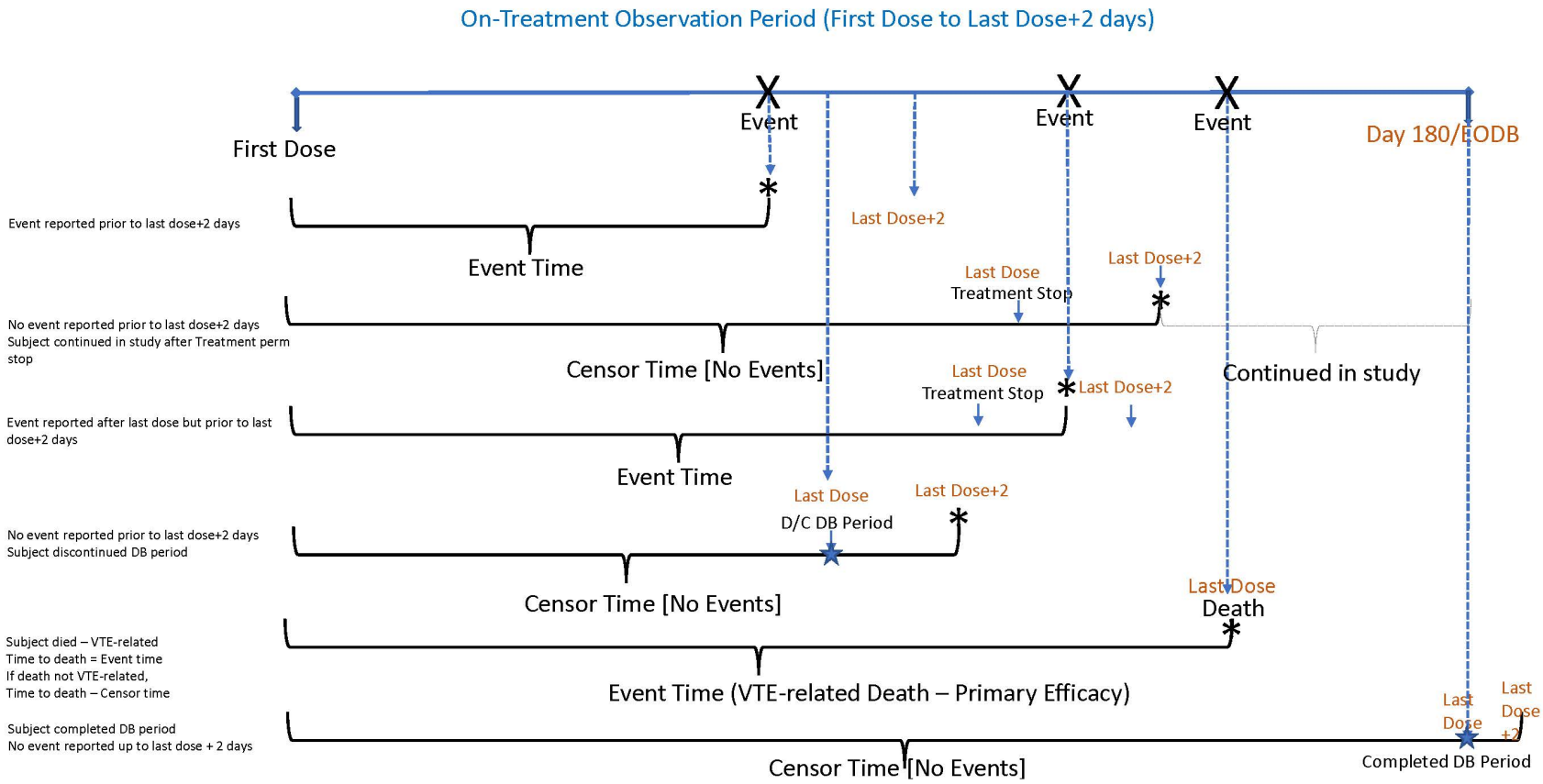


Figure 3: Post-Randomization observation period

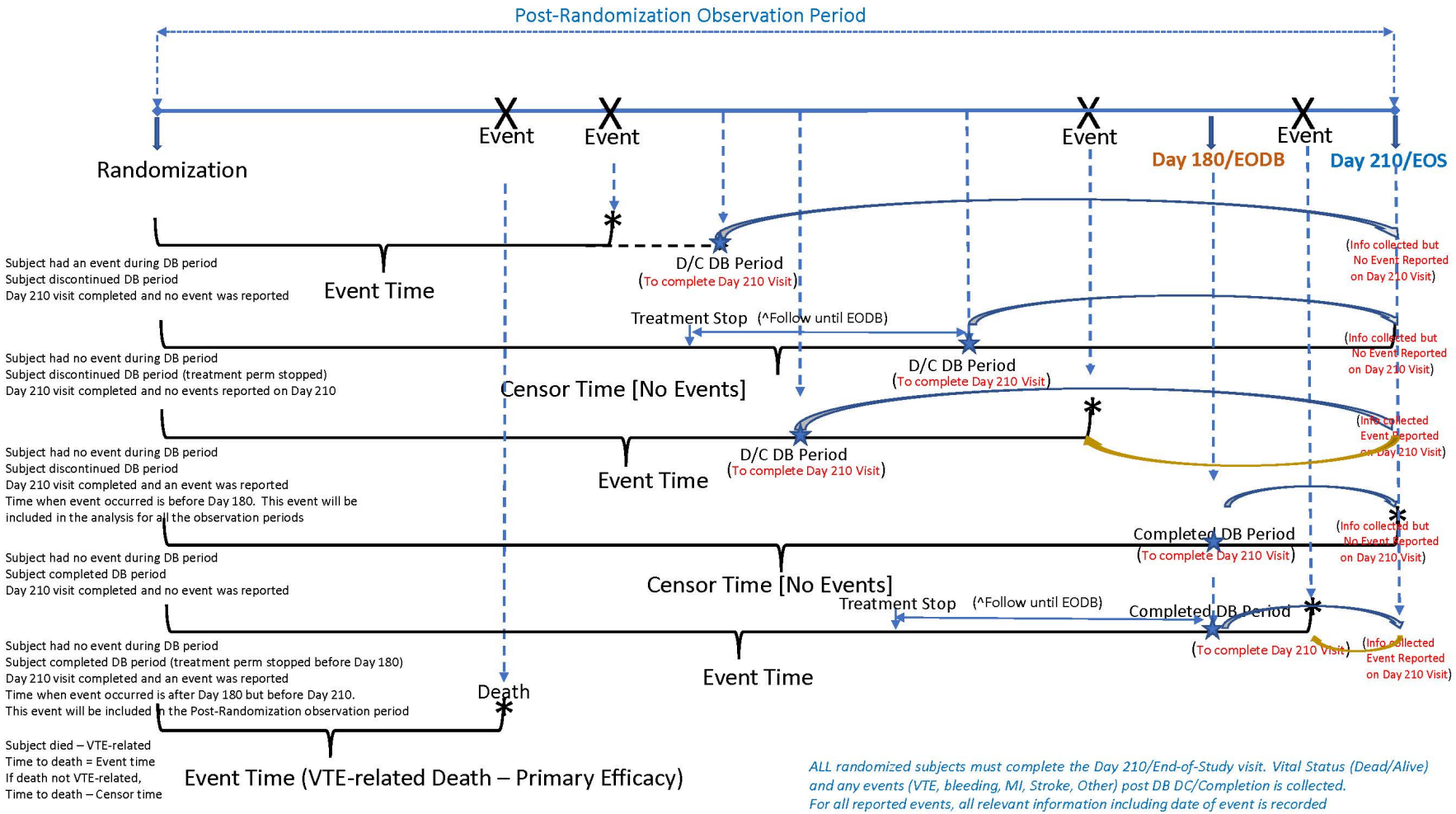
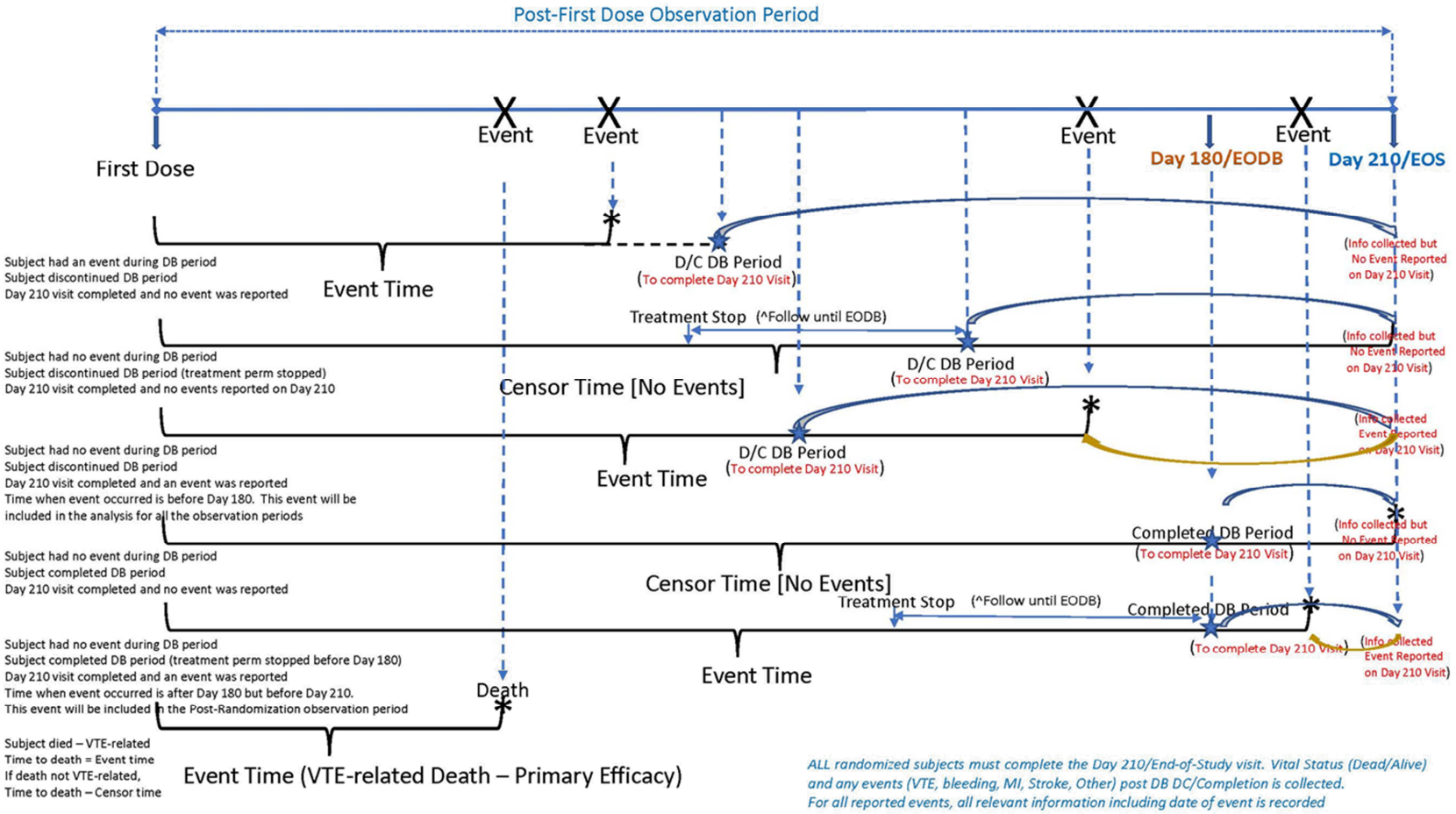


Figure 4: Post-Randomization observation period



ATTACHMENT: IDMC DATA PRESENTATION SPECIFICATION

The study SAP is used as the IDMC SAP however some of the rules for imputation times and missing dates due to data cutoffs were applied to generate the tables for the DMC meetings.

As per the IDMC Charter, three meetings were planned to be conducted for safety data and key efficacy data reviews. The IDMC meetings are scheduled at the availability of 25 % data (that is, when 25% of total planned subjects are randomized into the study and complete at least 30 days on study). Each of subsequent 2 meetings coincide with the enrollment of 50% and 75% of the planned subjects respectively who have been randomized and completed at least 30 days of study follow-up. An addition ad hoc review (fourth IDMC safety review meeting) was planned at the end of enrollment when 100% subjects are randomized.

Appropriate database was provided to IDMC statistical support group in accordance with the DMC Charter and established timeframes for each meeting.

For the fourth DMC meeting, symptomatic distal DVT was included in the primary efficacy composite endpoint in accordance with the amended protocol.

Rules

Analysis phase end date: min (death date, rand date+183, cutoff date)
Treatment end date imputed as: min (rand date+183, cutoff date, analysis phase end date) for ongoing subjects.

CNSR: the censor flag = 0 if event and censor flag = 1 if censor (no event)

Event date:
ADT: the date of event up to the time subject was in the study. That is, up to the subject's completion/withdrawal date (the Day 180 end date not defined for DMC).

Censor date:
Up-to-Day 180 observation period:
ADT for censored subjects = min (death date, rand date+183, cutoff date)

On-Treatment observation period:
ADT for censored subjects = min (death date, last dose+2), using the imputed TRTEDT