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An international, multicenter, randomized, double-blind, placebo controlled phase 3 trial investigating the efficacy and safety of rivaroxaban to reduce the risk of major thrombotic vascular events in patients with symptomatic peripheral artery disease undergoing lower extremity revascularization procedures

Vascular **O**utcomes stud**Y** of **A**SA alon**G** with rivaroxaban in **E**ndovascular or surgical limb **R**evascularization for peripheral artery disease (VOYAGER PAD)

Bayer study drug	BAY 59-7939/rivaroxaban		
Clinical study phase:	III	**Date:**	24 JULY 2019
Study No.:	BAY 59-7939 /17454	**Version:**	3.0
Authors:	PPD (Version 1.0, 2.0) PPD (Version 1.0, 2.0) PPD (Version 1.0) PPD (Version 2.0) PPD (Version 3.0)		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

ABI	Ankle Brachial Index
AE	Adverse Event
ALI	Acute Limb Ischemia
ASA	Acetylsalicylic acid; aspirin
BARC	Bleeding Academic Research Consortium
bid	Twice daily
CAD	Coronary Artery Disease
CI	Confidence Interval
CRF	Case Report Form
CV	Cardiovascular
e.g.	for example
eGFR	estimated Glomerular Filtration Rate
ECOD	Efficacy cut-off date
EOT	End-of-treatment
EQ-5D	European Quality of Life-5 Dimensions questionnaire
HR	Hazard ratio
ICAC	Independent Clinical Adjudication Committee
ICH	International Conference on Harmonisation
i.e.	id est (that is)
IDMC	Independent Data Monitoring Committee
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention-to-treat
IxRS	Interactive web/voice response system
KM	Kaplan Meier
LCEAD	Last Clinical Event Ascertainment Date
LDL	Low-density lipoprotein
MACE	Major adverse cardiac events
MALE	Major adverse limb events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NYHA	New York Hearth Association
od	Once daily
p	p-value
PAD	Peripheral Artery Disease
PT	Preferred Term
RRR	Relative risk reduction
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SOC	System Organ Class
TBI	Toe Brachial Index
TE	Treatment Emergent
TEAE	Treatment Emergent Adverse Events
TIMI	Thrombolysis in Myocardial Infarction

TLF	Tables, listings, and figures
USA	United States of America
vs.	versus
VTE	Venous thromboembolism
WIQ	Walking Impairment Questionnaire

1. Introduction

Peripheral artery disease (PAD) refers to the atherosclerotic obstruction of the major arteries supplying the lower extremities, sometimes also referred to as lower extremity artery disease. Atherosclerosis of the peripheral circulation, with underlying atheroma and chronic inflammation, leads to progressive occlusion of medium and large arteries, with additional risks of embolism or thrombus formation. Abrupt occlusions and plaque rupture may lead to acute complications such as acute limb ischemia (ALI), similar to an acute coronary syndrome event in the coronary circulation (Becker et al. 2011).

The hypothesis of the VOYAGER study is that rivaroxaban added to standard of care therapy of low-dose acetylsalicylic acid (ASA), has the potential to reduce the incidence of the major cardiovascular (CV) outcomes (i.e., CV death, myocardial infarction (MI), and ischemic stroke) as well as major lower limb vascular events (i.e. ALI and major amputation) in symptomatic PAD patients requiring lower extremity revascularization procedures.

This core statistical analysis plan (SAP) is based on the Global Integrated Clinical Study Protocol BAY 59-7939/17454 version 3.0 and contains definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety for the VOYAGER study. It provides a technical and detailed elaboration of the principal features of the planned analyses, e.g., censoring schemes for time-to-event variables. Amendments and/or appendices to this core SAP may be used to add additional analysis and provide more details on the coding guidelines, data-handling, and output tables and figures.

Titles, mock-ups, and programming instructions for all statistical output (tables, figures, and listings (TLF)) are provided in a separate TLF specifications document.

2. Study Objectives

The primary efficacy objective is:

- To evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of major thrombotic vascular events (defined as MI, ischemic stroke, CV death, ALI, and major amputation of a vascular etiology) in symptomatic PAD patients undergoing lower extremity revascularization procedure.

The secondary efficacy objectives are:

- To evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of MI, ischemic stroke, coronary heart disease mortality, ALI, and major amputation of a vascular etiology
- To evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of an unplanned index limb revascularization for recurrent limb ischemia (subsequent index leg revascularizations that were not planned or considered as part of the initial treatment plan at the time of randomization)

- To evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of vascular hospitalizations for a coronary or peripheral event (either limb) of a thrombotic nature
- To evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of MI, ischemic stroke, all-cause mortality, ALI, and major amputation of a vascular etiology
- To evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of MI, all-cause stroke, CV death, ALI, and major amputation of a vascular etiology
- To evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of all-cause mortality
- To evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of venous thromboembolic (VTE) events.

The primary safety objective of the study is:

- To evaluate the overall safety and tolerability of rivaroxaban added to ASA compared to ASA alone.

3. Study Design

This study is an international multicenter, randomized, placebo-controlled, double-blind, event-driven phase 3 study.

Following provision of informed consent, subjects who fulfill all inclusion criteria and meet none of the exclusion criteria will be treated with ASA 100 mg once daily (od) and randomly allocated by an interactive voice/web response system (IxRS) in a ratio of 1:1 to additional treatment with either rivaroxaban 2.5 mg or placebo twice daily (bid). The randomization will be stratified by type of procedure and use of clopidogrel (i.e., (i.) surgical vs. (ii) endovascular with clopidogrel vs. (iii) endovascular without clopidogrel). Treatments will be balanced within a country for each stratum by block randomization. Randomization and study treatment should commence as soon as possible but no later than 10 days after a successful qualifying revascularization procedure and once hemostasis has been assured. All randomized subjects will receive study medication (either rivaroxaban or placebo) and study ASA in a sufficient quantity until the next scheduled on-site visit and detailed instructions for its administration.

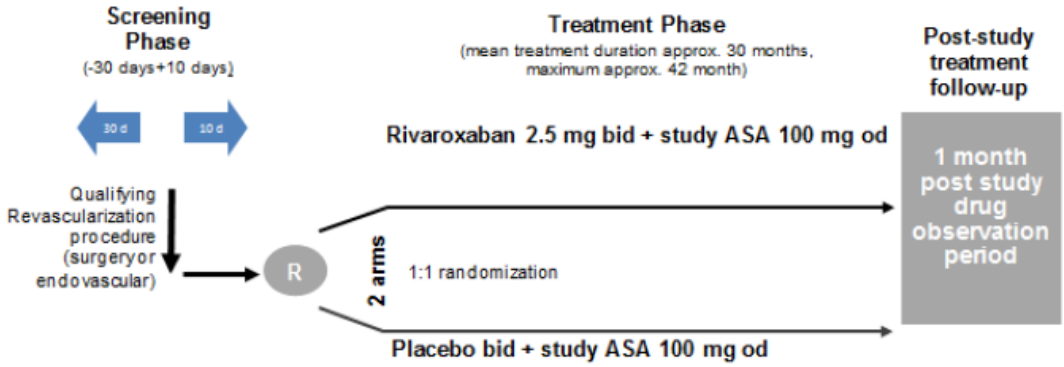
The study is event-driven, and thus, all subjects will be treated (or followed-up in the case of permanent discontinuation of study medication) until the end of treatment (EOT) visit. It is estimated that approximately 6,500 subjects (3,250 per treatment group) are needed to be enrolled in order to have 1,015 subjects experiencing a confirmed primary efficacy outcome event. Due to the event-driven study design, no firm treatment duration can be stipulated for an individual subject. The estimated maximum treatment period for an individual subject is approximately 42 months, and the mean treatment duration is expected to be approximately 30 months. However, this duration may vary depending on the recruitment rate as well as the primary event rate.

Subjects who have discontinued study drug treatment prematurely should continue to be followed according to the regular visit schedule, and study efficacy outcome events, bleeding events and vital status must be assessed in these subjects until the end of the study via either clinic visits or telephone contacts.

Throughout the study and at all on-site visits, subjects will be assessed for the occurrence of study efficacy outcome events and bleeding events. Suspected clinical study outcomes (study efficacy outcome and bleeding events) will be assessed independently by an Independent Clinical Adjudication Committee (ICAC) blinded to treatment allocation, and the adjudicated results will be the basis for the final study analyses.

There will be one formal interim analysis, which will occur when approximately 67% of the planned primary efficacy outcomes have accrued and adjudicated.

A simplified schematic of the study design is provided in the following figure:



4. General Statistical Considerations

4.1 General Principles

All variables will be summarized using descriptive statistical methods. The number of patients with data available and missing, mean, standard deviation, minimum, quartiles, median, and maximum will be provided for continuous variables, as appropriate. Frequency tables will be provided for categorical variables. The decision rules will be based on one-sided superiority testing unless otherwise specified, but in addition to the one-sided p-values from the logrank test, two-sided p-values will be reported according to general conventions. The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

4.2 Handling of Non-compliance to Study Treatment or Follow up

A randomized subject who permanently discontinues rivaroxaban or rivaroxaban placebo before their planned EOT Visit for any reason is defined as having had a permanent discontinuation of study medication (including subjects who were randomized but never

started taking any study medication). The reason for permanent discontinuation of study medication will be collected and summarized.

A subject will be considered as lost to follow-up for analysis purposes if contact is not obtained with the subject despite all possible efforts by the site, and the subject's vital status is not obtained and documented in the database at the end of the study.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the case report form (CRF) including best estimate dates of site investigators collected in the clinical database.

Missing or incomplete post-randomization event dates

All efforts will be made to collect complete data for all subjects randomized in this study including visits by telephone contact. Subjects will be followed to the study end and all required data will be collected, regardless of their compliance with study medications or visits.

When an event date is not complete, the date will be estimated according to the following rules but not earlier than randomization date,

- If only the onset day is missing, but the month and year are available:
    - If the month and year are the same as the efficacy cut-off date (ECOD), impute the date as mean of the first day of the onset month/year and the ECOD (rounded up).
    - Otherwise if the month and year are the same as the last contact date alive (see Appendix A), impute the date as mean of the first day of the onset month/year and the last contact date alive (rounded up). For death event, the last contact alive date +1 day will be used as the death date.
    - Otherwise impute the event date as maximum of the date of randomization + 1 and day 15 of the onset month and year.
- If the onset day and month is missing, but the year available:
    - The minimum possible date is maximum of randomization date + 1 days and January 1st of the onset year.
    - The maximum possible date is the minimum of the ECOD and last contact date alive and December 31th of the onset year.
    - Impute the event date as mean of the minimum possible date and the maximum possible date (rounded up).
    - For subjects who experienced death in the same year as last contact alive date, the last contact alive date +1 day will be used as the death date.
- If the onset date is complete missing, the onset date will be imputed with the randomization date + 1 days.
- For subjects who experienced death during the study and the death date is completely missing, the last contact alive date + 1 day will be used to impute death date. If the last contact alive date is missing, the death date will be imputed as ECOD.

4.4 Interim Analyses and Data Monitoring

The Independent Data Monitoring Committee (IDMC) will monitor the study for greater than expected efficacy and for safety. There will be one formal pre-planned interim analysis to assess greater than expected efficacy, which will be performed when approximately 67% of the planned primary efficacy outcome events (~680) have accrued and are adjudicated. Based on that analysis, the study may be stopped early, if there is overwhelming superiority of rivaroxaban ($p<0.001$, 2-sided) for the primary efficacy endpoint (following the Haybittle-Peto approach) (Haybittle 1971]. Details on the approach to the interim analyses and refinement of decision rules are specified in the IDMC charter.

4.5 Data Rules

4.5.1 Analysis Dates

For the study, the following date and time window are of relevance for the analysis:

- Efficacy cut-off date:

  The trial is designed to be terminated when 1015 patients have experienced a confirmed primary efficacy outcome event. The ECOD is a predicted common date when at least 1015 primary efficacy outcomes are expected to have occurred. It is the last calendar date acceptable for counting events for the primary analysis.

- Trial close-out window:

  The time period when all subjects return to the clinic for an EOT visit. All randomized subjects should return for their EOT visit after the ECOD.

For each subject, the following individual dates are of relevance for analysis:

- Randomization date:

  The date of randomization as recorded in the IxRS system.

- EOT Visit date:

  The date of the EOT visit. If subjects do not have an EOT visit, the date will be missing.

- Date of last contact:

  The date of the last documented contact with the subject or a third party (including data on subject survival status, see Appendix A for details).

- Date of first dose of study treatment:
  The date of the first dose of rivaroxaban or rivaroxaban placebo, defined as:
  - Date of first dose from the appropriate CRF page capturing the study medication (rivaroxaban or rivaroxaban placebo) if this date is complete.
  - Date of the earliest logically possible dose of study medication (rivaroxaban or rivaroxaban placebo) administration in cases where the date of first dose is missing or incomplete. See Appendix D for details of the imputation rules.

- Date of last dose of study treatment:

The date of the last dose of rivaroxaban or rivaroxaban placebo, defined as:

- Date of last dose from the appropriate CRF page capturing the study medication (rivaroxaban or rivaroxaban placebo) if this date is complete.
- Date of the latest logically possible dose of study medication (rivaroxaban or rivaroxaban placebo) administration in cases where the date of last dose is missing or incomplete. See Appendix D for details of the imputation rules.

4.5.2 Data Scopes

All analyses are based on two elements:

1) *analysis set*, which specifies which subjects will be included in an analysis; and

2) *data scope*, which specifies the time window within which data will be included in an analysis.

This section describes the coverage of the event *data scopes* used for the statistical analyses. *Analysis sets* are described in Section 5.

Data scope according to intention-to-treat principle (ITT)

The ITT data scope includes outcome events observed from randomization date until the ECOD. Events occurring after the ECOD will not be counted for primary analysis. This ITT data scope will be applied mainly to the analyses of efficacy variables.

Data scope according to treatment (on-treatment)

The on-treatment data scope will include all outcome events observed from randomization until 2 days following permanent discontinuation of the study drug. This on-treatment data scope will be applied mainly to the analyses of safety variables (e.g. bleeding).

Data scope according to overall study duration for sensitivity analysis

The overall study duration data scope will include all outcome events observed from randomization until the last contact/visit. This data scope will be applied for sensitivity analysis only.

4.5.3 Censoring rules for time-to-event variables

All efforts will be made to collect complete data for all subjects randomized in this study including visits by telephone contact.

Censoring rules for analyses according to the ITT principle

The censoring rule for time to first event analyses depends on the type of endpoint, thereby distinguishing between clinical events endpoints (primary efficacy composite and component, secondary efficacy and bleeding events) and CV-death / all-cause mortality.

	Primary efficacy composite and components other than CV-death	All-cause mortality, CV-death
If the subject was randomized but has no post-randomization clinical event ascertainment date the subject will be censored :	At the randomization date + 1 day	Earlier of last contact alive date or ECOD If no last contact alive date, use the randomization date +1 day
Else, if the subject has withdrawn from the study but objected to further data collection the subject will be censored :	At the earlier date of the last clinical event ascertainment date (LCEAD), date of objection to further data collection or ECOD	Earlier of last contact alive date from public sources or ECOD If no last contact alive date from public sources, use the earlier date objection to further data collection or ECOD
Otherwise, the subject will be censored :	At the earlier date of last clinical event ascertainment date, date when patient died or ECOD	At the earlier date of last contact alive date or ECOD

Censoring rules for analyses according to the on-treatment principle

For on-treatment analyses (primary analysis for time to bleeding events, sensitivity analysis for primary efficacy endpoint and all secondary efficacy endpoints), patient with at least one dose of study medication and without documentation of an event within the on-treatment data scope will be censored similarly to the ITT data scope except that the date of last dose of study treatment + 2 days will be used as the cap for the time scope instead of ECOD.

Censoring rules for analyses according to the overall study duration principle

Above censoring rules for ITT data scope apply except that the date of last clinical event ascertainment or last contact alive will be used as the cap for the time scope instead of ECOD.

See Appendix A for additional details.

4.6 Determination of sample size

The study is event-driven and it is estimated that approximately 6,500 patients (3,250 per treatment group) need to be randomized in order to have 1,015 patients experiencing a confirmed primary efficacy outcome event. This number of events will allow the demonstration of superiority of rivaroxaban compared to placebo with regard to the primary outcome with a power of 90% and a one-sided level of significance α=0.025 under the following assumptions:

- The effect size (Hazard Ratio (HR)) for rivaroxaban plus ASA vs. ASA alone is HR=0.80.
- The annualized event rate in the control arm is approximately 7.5% per year.
- The rate of patients with permanent discontinuation of study drug (rivaroxaban plus ASA switching to ASA alone or an equally effective treatment regimen) is approximately 5.5% 1st year, 8% 2nd year, 12% 3rd year (4% 1st half year + 8% 2nd half year), and 8% every half year afterwards.

- The rate of patients lost to follow-up or with non-CV death is approximately 1.5% per year.
- The duration of the enrollment period is 18 months (approximately 15% 1st 6 months, 30% 2nd 6 months, 55% 3rd 6 months) and 2 years of follow-up from last patient-randomized until the ECOD.

The number of patients enrolled may be adjusted and the study duration may be adapted based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study.

Sample size estimation was based on PASS 11 (Hintze 2011).

5. Analysis Sets

5.1 Assignment of analysis sets

All subjects who have been randomized in the study are valid for assignment to analysis sets.

5.1.1 Intention-to-treat (ITT) analysis set

The intention-to-treat analysis set, also termed full analysis set in the International Conference on Harmonization (ICH) E9 guideline, will include all randomized subjects. Subjects will be categorized to the treatment group to which they were assigned by the IxRS; i.e., they will be analyzed as randomized.

5.1.2 Safety analysis set (SAF)

The SAF will include all randomized subjects who received at least one dose of study medication (rivaroxaban or rivaroxaban placebo). Subjects will be categorized to the group to which they were assigned by the IxRS unless the incorrect treatment was received throughout the study. In this case, subjects will be analyzed for safety as actually treated.

The planned analyses for the primary and secondary efficacy and safety variables are summarized in but not limited to Table 1 below

Table 1 Sketch of the planned primary and secondary efficacy and safety analyses

Endpoint	Analysis Type	Analysis Set (population)[1]	Data Scope[2]	Censoring Rule[3]	Analysis Method
Efficacy					
Primary					
Composite of MI, ischemic stroke, CV death, Acute Limb Ischemia, major amputation due to a vascular etiology	Main	ITT	ITT	ITT	Stratified log-rank test, HR estimates from stratified Cox PH model, KM plot
	Sensitivity	ITT	ITT	ITT	Cox PH model with *no stratification*; Cox PH model with *actual* stratification; robust proportional hazard estimator; tipping point analysis
		SAF	On-treatment	On-treatment	Stratified log-rank test, HR estimates from stratified Cox PH model, KM plot
		ITT	Overall study duration	Overall study duration	Stratified log-rank test, HR estimates from stratified Cox PH model, KM plot
	Subgroup	ITT	ITT	ITT	HR estimates from stratified Cox PH model[4], forest plot
		SAF	On-treatment	On-treatment	HR estimates from stratified Cox PH model[4], forest plot
Secondary					
All secondary efficacy variables. For the list of secondary efficacy variables, see section 6.2.2.	Main	ITT	ITT	ITT	Stratified log-rank test, HR estimates from stratified Cox PH model, KM plot
	Sensitivity	SAF	On-treatment	On-treatment	Stratified log-rank test, HR estimates from stratified Cox PH model, KM plot

Endpoint	Analysis Type	Analysis Set (population) [1]	Data Scope[2]	Censoring Rule[3]	Analysis Method
		Safety			
Primary					
TIMI major bleeding	Main	SAF	On-treatment	On-treatment	Stratified Cox PH model, KM plot
	Supportive	SAF	ITT	ITT	Stratified Cox PH model, KM plot
		SAF	Overall study duration	Overall study duration	Stratified Cox PH model, KM plot
	Subgroup	SAF	On-treatment	On-treatment	Stratified Cox PH model[4], forest plot
Secondary					
ISTH major bleeding BARC type 3b and above bleeding	Main	SAF	On-treatment	On-treatment	Stratified Cox PH model, KM plot

Note: Details of the planned analyses are provided in section 6.

1. Intention-to-treat (ITT) analysis set – all randomized subjects. Treatment assigned as randomized; Safety analysis set (SAF) – all randomized subjects who received at least one dose of study medication. Treatment assigned as treated. See section 5.1 for details.
2. ITT data scope – all outcome events observed from randomization until efficacy cut-off date; On-treatment data scope – all outcome events observed from randomization until 2 days following permanent discontinuation of the study drug (rivaroxaban or rivaroxaban placebo). See section 4.5.2 for details. Overall study duration scope - all outcome events observed post randomization including post-study treatment follow-up.
3. See section 4.5.3 and Appendix A for details regarding the censoring rules according to each data scope.
4. Not stratified for subgroups related to type of procedure and clopidogrel use. See sections 6.2.4, 6.2.9 and 6.4.5 fordetails.

6. Statistical Methodology

6.1 Population characteristics

6.1.1 Disposition

The following will be tabulated overall and/or by treatment group:

- Study sample sizes (All enrolled subjects, ITT, and SAF)
- Study sample sizes by region, country, and site
- Subject disposition
- Number of subjects and primary reasons for screening failures (only overall)
- Number of subjects and primary reasons for permanent discontinuation of study medication (by treatment group and overall for ITT and SAF)
- Number of subjects and primary reasons for discontinuation from intended study treatment period (by treatment group and overall for ITT and SAF)

6.1.2 Demographics

The following demographic and baseline characteristics will be summarized by treatment group and overall in ITT and SAF. Summary statistics will be presented for metric variables. Frequency tables will be presented for categorical variables. Subjects will be considered fragile if age >75 years or weight ≤50 kg or baseline eGFR <50 mL/min.

- Age (<55; ≥55 to <65; ≥65 to ≤75; >75 years)

- Age (<65; ≥65 to <75; ≥75 years)
- Age (<65; ≥65 to <85; ≥85 years)
- Sex (male, female)
- Race (White; Black or African American; Asian; American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; Not reported; Multiple)
- Type of qualifying procedure and clopidogrel use, per IxRS assignment (surgical; endovascular with clopidogrel; endovascular without clopidogrel)
- Qualifying revascularization procedure per IxRS (surgical; endovascular)
- Geographic Region (North America, Western Europe, Eastern Europe, Asia Pacific, South America, see Appendix B for details)
- Geographic Region (US, non-US)
- Weight (≤60 kg; >60 kg)
- estimated Glomerular Filtration Rate (eGFR) (<60 ml/min/1.73m^2 , ≥60 ml/min/1.73m^2)
- eGFR (<15 ml/min/1.73m^2, ≥15 to <30 ml/min/1.73m^2, ≥30 to <60 ml/min/1.73m^2, ≥60 ml/min/1.73m^2)
- eGFR (<30 ml/min/1.73m^2, ≥30 to ≤50 ml/min/1.73m^2, >50 to ≤80 ml/min/1.73m^2, >80 ml/min/1.73m^2)
- Fragile subjects (yes, no)
- Qualifying revascularization procedure, actual (surgical; endovascular including hybrid)
- Clopidogrel use in relation to qualifying revascularization procedure (yes, no)
- Time from qualifying revascularization procedure to randomization, actual (≤median, >median)
- Type of qualifying procedure and clopidogrel use, actual (surgical; endovascular including hybrid with clopidogrel; endovascular including hybrid without clopidogrel)
- Clopidogrel use continued after randomization (none, ≤30 days, >30 days)
- Prior coronary artery disease (CAD) (yes; no)
- Prior MI (yes; no)
- Prior limb revascularization (yes; no)
- Carotid artery disease history (yes; no)
- Critical limb ischemia (yes; no)
- Intermittent claudication present within past 12 months (yes; no)
- History of heart failure (yes; no)
- Classification of heart failure (NYHA class I, class II, class III, class IV)

- Diabetes mellitus (yes; no)
- Smoking status (former, never, current)
- Hypertension (yes; no)
- Hyperlipidemia (yes; no)
- Baseline Ankle Brachial Index (ABI) (at Month 1 visit) (≤0.80; >0.80)
- Baseline Toe Brachial Index (TBI) (at Month 1 visit) (≤0.60; >0.60)

In addition, age, days from actual qualifying revascularization procedure to randomization and baseline Low-density lipoprotein (LDL) will be treated as continuous variable and summarized descriptively. Other baseline characteristics may be added.

6.1.3 Medical history

Medical history will be presented by the pre-specified terms as listed in the CRF. Medical history data will be evaluated by frequency tables, showing the number of subjects with medical history findings (i.e., listed conditions of previous diagnoses, diseases, or surgeries based on the CRF) that started before signing of the informed consent and that are considered relevant to the study.

6.1.4 Protocol Deviations

A summary of protocol deviations related to in- and exclusion criteria will be given by frequency tables. The summary will be based on ITT.

6.1.5 Prior and Concomitant Medications

Prior and concomitant medications will be presented by the pre-specified terms as listed in the CRF. Frequency tables by type of medication will be provided for prior medications prior to randomization and for concomitant medication post-randomization. The summaries will be by treatment group and overall based on ITT.

6.1.6 Extent of Exposure and Compliance

All summaries related to intake of study medication (rivaroxaban or rivaroxaban placebo) will be by treatment group based on SAF.

The treatment duration (date of last study medication- date of first study medication+1 day) will be summarized descriptively. Additionally the number of subjects by treatment duration category will be given (≤3 months, >3-≤6 months, >6-≤9 months, >9-≤12 months, >12-≤18 months, >18-≤24 months, >24 months).

The time on study medication (treatment duration excluding days off study medication) will be calculated and summarized descriptively.

The number of tablets taken will be summarized descriptively, as well as corresponding extent of exposure (number of tablets taken*dose).

Compliance (or adherence, defined as 100*number of tablets taken / number of tablets planned) will be presented by visit as entered in the CRF and summarized for the whole study. The number of subjects with at least 80% compliance will be presented.

6.2 Efficacy

6.2.1 Primary efficacy variable

The primary efficacy variable is the time from randomization to first occurrence of any of the components of the composite outcome, including:

- MI
- ischemic stroke
- CV death
- ALI
- major amputation due to a vascular etiology

6.2.2 Secondary efficacy variables

The secondary efficacy variables of this study are:

- time from randomization to the first occurrence of MI, ischemic stroke, coronary heart disease mortality, ALI, and major amputation of a vascular etiology
- time from randomization to the first occurrence of an unplanned index limb revascularization for recurrent limb ischemia (subsequent index leg revascularization that was not planned or considered as part of the initial treatment plan at the time of randomization)
- time from randomization to the first occurrence of hospitalization for a coronary or peripheral cause (either lower limb) of a thrombotic nature
- time from randomization to the first occurrence of MI, ischemic stroke, all-cause mortality, ALI, and major amputation of a vascular etiology
- time from randomization to the first occurrence of MI, all-cause stroke, CV death, ALI, and major amputation of a vascular etiology
- time from randomization to the first occurrence of all-cause mortality
- time from randomization to the first occurrence of VTE events

6.2.3 Other efficacy variables

The other efficacy variables of this study are:

- time from randomization to the first occurrence of all subsequent limb revascularizations of the lower extremity that were not planned or considered as part of the initial treatment plan at the time of randomization.
- time from randomization to the first occurrence of all-cause amputations;
- patient reported outcomes using disease and non-disease specific questionnaires (European Quality of Life-5 Dimensions questionnaire (EQ-5D) and Walking Impairment Questionnaire (WIQ)).
- serial changes in limb hemodynamics (ABI and TBI).

6.2.4 Subgroup variables

The following subgroup analyses based on baseline and demographic characteristics are planned for the treatment comparisons of the primary efficacy and safety outcomes:

- Age (<55; ≥55 to <65; ≥65 to ≤75; >75 years)
- Age (<65; ≥65 to <75; ≥75 years)
- Age (<65; ≥65 to <85; ≥85 years)
- Sex (male; female)
- Race (White; Black or African American; Asian; Other)
- Type of qualifying procedure and clopidogrel use, per IxRS assignment: (surgical; endovascular with clopidogrel; endovascular without clopidogrel)
- Qualifying revascularization procedure per IxRS (surgical; endovascular)
- Geographic Region (North America; Western Europe; Eastern Europe; Asia Pacific; South America, see Appendix B for details)
- Geographic Region (US, non-US)
- Weight (≤60 kg; >60 kg)
- estimated Glomerular Filtration Rate (eGFR) (<60 ml/min/1.73m^2 , ≥60 ml/min/1.73m^2)
- eGFR (<15 ml/min/1.73m^2, ≥15 to <30 ml/min/1.73m^2, ≥30 to <60 ml/min/1.73m^2, ≥60 ml/min/1.73m^2)
- eGFR (<30 ml/min/1.73m^2, ≥30 to ≤50 ml/min/1.73m^2, >50 to ≤80 ml/min/1.73m^2, >80 ml/min/1.73m^2)
- Fragile subjects (yes, no)
- Qualifying revascularization procedure, actual (surgical; endovascular including hybrid)
- Clopidogrel use in relation to qualifying revascularization procedure (yes, no)
- Type of qualifying procedure and clopidogrel use, actual (surgical; endovascular including hybrid with clopidogrel; endovascular including hybrid without clopidogrel)
- Clopidogrel use continued after randomization (<30 days, >=30 days, none)
- Prior coronary artery disease (CAD) (yes; no)
- Prior MI (yes; no)
- Prior MI and age < 65 years (yes, no)
- Prior MI and reduced renal function, i.e., eGFR <60 mL/min (yes, no)
- Carotid artery disease history (yes; no)
- Prior limb revascularization (yes; no)
- History of heart failure (yes; no)

- Diabetes mellitus(yes; no)
- Smoking status (former, never, current)
- Hypertension (yes; no)
- Hyperlipidemia (yes; no)
- Baseline (Month 1 visit)
    - ABI ≤0.80 or TBI ≤0.60;
    - ABI >0.80 and TBI >0.60;
    - TBI and ABI not done

6.2.5 Analysis of the primary efficacy variable

The primary analysis will be based on the time from randomization to the first occurrence of any of the components of the primary efficacy outcome (independently adjudicated), using the ITT analysis set and ITT data scope.

The null hypothesis will be:

> $H_{0,\,PE}$: $S_R(t) = S_A(t)$ for all time points t ≥0, (i.e., "there is no difference between the rivaroxaban added to ASA group and the ASA alone group regarding the primary efficacy outcome for all time points"),

and the one-sided alternative hypothesis will be:

> $H_{1,\,PE}$: $S_R(t) > S_A(t)$ for at least one time point t ≥0, and $S_R(t) \geq S_A(t)$ for all time points t ≥0, (i.e., "there is a difference between the two groups in favor of rivaroxaban regarding the primary efficacy outcome for at least one time point"),

where S_R denotes the survival function of the rivaroxaban added to ASA group and S_A denotes the survival function of the ASA alone group.

The rivaroxaban added to ASA group will be compared to the ASA alone group using a log-rank test stratified by type of procedure and clopidogrel use ((i.) surgical vs. (ii.) endovascular with clopidogrel vs. (iii.) endovascular without clopidogrel per IxRS assignment) with treatment as a fixed factor. Superiority of rivaroxaban over placebo will be declared, if the associated one-sided null hypothesis is rejected in favor of rivaroxaban at the 2.5% significance level.

Kaplan-Meier (KM) estimates of cumulative risk and cumulative hazard functions will be provided to evaluate the timing of event occurrence in the different treatment groups and the consistency of the respective treatment effects for all time points.

The following SAS program code will be used for the log-rank test and Kaplan-Meier estimates:

```
PROC LIFETEST DATA = <dataset> ALPHA=0.05 METHOD=KM NELSON;
  STRATA stratumn / GROUP=trtgrpn TEST=(LOGRANK) TREND;
  TIME ttevalue * ttecnsr(0);
RUN;

/*
where
dataset  = name of dataset including all ITT subjects
trtgrpn  = variable coding randomized treatment group
ttevalue = time to first occurrence of primary efficacy outcome event
ttecnsr  = censoring index (0 = right-censored, 1 = event)
stratumn = variable for stratification factor */
```

The relative risk reduction (RRR) will be estimated using a Cox proportional hazards (Cox PH) model, stratified by type of procedure and use of clopidogrel per IxRS assignment, with treatment as the only covariate. The point estimate and corresponding 95% confidence interval (CI) for the hazard ratio (HR, rivaroxaban added to ASA vs. ASA alone) will be reported. The plausibility of proportional hazards assumption will be assessed by visually comparing the plot of the log of cumulative hazard between treatments and by additionally adding a treatment by logarithm-transformed time interaction into the Cox PH model.

The following SAS program code will be used for the Cox proportional hazards model:

```
PROC PHREG DATA = <dataset>;
  MODEL ttevalue * ttecnsr(0) = trtgrpn / RL TIES=EFRON ALPHA=0.05;
  STRATA stratumn;
RUN;

/*
where
dataset  = name of dataset including all ITT subjects
trtgrpn  = variable coding randomized treatment group
ttevalue = time to first occurrence of primary efficacy outcome event
ttecnsr  = censoring index (0 = right-censored, 1 = event)
stratumn = variable for stratification factor
*/
```

Additional procedure options controlling the output may be added to the program codes.

6.2.6 Analysis of secondary efficacy variables

If the primary efficacy outcome is statistically significant, the secondary efficacy outcomes will be tested in a sequential manner according to the order as listed in Section 6.2.2 with one-sided alpha of 0.025. If an individual test during any step is not statistically significant, further treatment comparison may continue (i.e., reporting of p-values) but significance will not be claimed. This hierarchical testing procedure will control the global Type 1 error level.

The analysis of the secondary variables will be based on the ITT analysis set and ITT data scope, including events as adjudicated by the ICAC or reported by investigators if not being adjudicated.

The statistical hypotheses for the secondary efficacy outcomes are defined similarly as for the primary efficacy outcome. The analysis methods will be similar to those described for the primary efficacy outcome.

6.2.7 Analysis of other efficacy variables

The analysis of the other variables will be based on the ITT analysis set and ITT data scope, including events as adjudicated by the ICAC or reported by investigators if not being adjudicated. These analyses will be considered exploratory.

The analysis methods will be similar to those described for the primary efficacy outcome except for patient reported outcomes.

For EQ-5D and WIQ, the change from baseline of the mobility domain of EQ-5D and each domain of WIQ (pain [PAD specific question and Q1 of differential diagnosis], distance, speed, stair climbing) will be analyzed using an ANCOVA model with baseline value as a covariate and treatment as the only fixed effect. Baseline is the last measurement prior to or at randomization.

For limb hemodynamics (ABI and TBI separately), the changes from baseline will be analyzed using an ANCOVA model with baseline value as a covariate and treatment as the only fixed effect. Since the ABI and TBI is expected to improve after qualifying revascularization and decrease gradually over time, baseline value is defined as the measurement at month 1 visit.

Summary statistics of EQ-5D, WIQ and ABI and TBI actual and change from baseline values will also be provided by visit.

6.2.8 Exploratory analysis

Exploratory analysis of the individual components of the primary and secondary efficacy outcomes will be analyzed similarly to the primary efficacy outcome. Composite outcomes major adverse cardiac events (MACE, ie. CV death, MI and ischemic stroke) and major adverse limb events (MALE, i.e. ALI and major amputation due to a vascular etiology) will be analyzed similarly to the primary efficacy outcome.

To account for the multiple components of the primary efficacy endpoint, all event analysis will be evaluated in ITT data scopes and on-treatment data scopes by fitting frailty model with gamma distribution of the shared frailty terms as an extension of the Cox accounting for correlation of the events within a subject (see Hougaard, 2000; Wienke, 2011; Austin, 2017), with treatment as the only covariate. In addition, model with log-normal distribution of the shared frailty terms will be fitted. Another extension of the Cox model is the Andersen-Gill model, which assumes that each recurrence is an independent event (Andersen, 1982). To account for the intra-subject correlation, models with robust standard error estimator will be fitted according to Lin's method (Lin et al. 2000).

The primary efficacy endpoint will be explored for the following subgroups

- Qualifying endovascular techniques
  - Balloon angioplasty (drug-coated and not coated), yes/no

  - Angioplasty with stent (bare metal, drug-coated, covered) yes/no
  - Atherectomy
  - Thrombolysis
- Time from qualifying revascularization procedure to randomization (<median; >=median)
- History of lower limb amputation
  - Major ischemic amputation with or without other amputation
  - Minor ischemic amputation with or without non-ischemic amputation
  - Nonischemic amputation only
  - No amputation

The frequency will be presented descriptively (and with forest plots). The hazard ratio for the treatment effect will be estimated separately within each level of a subgroup using the Cox proportional hazards model without stratification.

The following variable will also be explored:

- Time from randomization to the first occurrence of MI types
- Any revascularization after randomization regardless of the side as reported by the investigator
- Any index leg revascularization as reported by the investigator

In addition, ABI and TBI will be further explored to understand the effect of natural history and drug effect on hemodynamics. Examples include:

- Change in ABI and TBI post randomization excluding values after subsequent revascularization by subgroup (endovascular versus surgical)
- Change in ABI and TBI post randomization in patients with subsequent intervention versus those who do not undergo subsequent intervention

To explore the robustness of the treatment effect over time, landmark analyses will be performed for the primary endpoint according to landmark periods of randomization to 3-month, 3-month to 1-year and 1-year to the end of treatment phase and randomization to 6-month, 6-month to 1 year and 1-year to end of treatment phase (Van Houwelingen 2007). Additional time point after 1-year may be added depending on the actual study duration. For each landmark period, the hazard ratio will be estimated using a Cox PH model stratified by type of procedure and use of clopidogrel (per IxRS assignment) with treatment as the only covariate, the corresponding 95% CI will be provided, and Kaplan-Meier (KM) plot of cumulative risk will be generated, respectively. The hazard ratio will also be calculated for the two main components (MACE versus MALE) of the primary endpoint.

6.2.9 Subgroup analysis

Patients with actual qualifying revascularization procedure

In addition to the stratification based on the IxRS assignment, the study will be analyzed based on the actual qualifying revascularization procedure and actual clopidogrel use in relation to qualifying revascularization as follows:

- surgical,
- endovascular including hybrid with clopidogrel,
- endovascular including hybrid without clopidogrel.

Patients with hybrid procedures are classified as endovascular revascularization. We plan to determine the treatment effect among patients in each of the above strata (actual classification). Treatment groups will be compared using Cox proportional hazards model with treatment as a covariate for the primary (also the individual components) and secondary efficacy endpoints, using the ITT analysis set and ITT data scope. The point estimate and corresponding 95% CI for the hazard ratio (HR, rivaroxaban added to ASA vs. ASA alone) will be reported. Additional analyses on other endpoints may be performed based on both per IxRS assignment and actual type of qualifying procedure and clopidogrel use.

Other subgroups

The analyses for the other subgroups (as defined in section 6.2.4) will be performed based on the same analysis sets and data scopes as in the main analyses for the primary efficacy outcome (also the individual components). The results will be presented descriptively (and with forest plots). The hazard ratio for the treatment effect will be estimated separately within each level of a subgroup variable using the Cox proportional hazards model stratified by type of procedure and clopidogrel use (per IxRS assignment) (except for subgroups related to qualifying revascularization procedure or clopidogrel use) with treatment as a covariate.

Additionally, homogeneity of treatment effect in subgroups, both in magnitude and direction, will be assessed by adding a covariate for the subgroup variable and the corresponding treatment-subgroup interaction to the respective Cox proportional hazards model. This further investigation includes the likelihood ratio test proposed by Gail to test for qualitative interaction (Gail et al. 1985).

As the number of subgroup analyses may be large, the probability of observing at least one spurious interaction is high despite the lack of a biological or pharmacological basis for expecting an interaction. Thus, any interaction with a p-value below the 5% type I error level in the analysis of primary outcome will be interpreted as “flag” to prompt further investigation into the consistency of the pattern within secondary and related outcomes.

The analyses for the subgroups as defined in section 6.2.4 will also be performed based on the same analysis set and data scope as in the main analysis for the secondary efficacy outcomes (also the individual components).

6.2.10 Sensitivity analyses

To support the primary study results and to assess the robustness of the primary analysis, several sensitivity analyses will be performed.

The primary efficacy variable will be analyzed based on the ITT analysis set and ITT data scope

- using the Cox proportional hazard model with actual stratification
- using the Cox proportional hazard model without stratification
- Using a proportional hazards estimator that is robust to departures from proportional hazard (Boyd et al. 2012)

The primary efficacy outcome (also the individual components) as adjudicated by ICAC will also be analyzed using the same Cox PH model as described in section 6.2.5 based on SAF and on-treatment data scope. The same analysis will be repeated based on ITT analysis set and overall study duration including post-study treatment follow-up. All subjects who are event free will be censored at the date of last clinical event ascertainment or last contact.

The primary efficacy outcome as reported by investigator will be analyzed similarly based on the ITT analysis set and ITT data scope.

For the individual components of investigator reported primary efficacy outcome see Appendix E.

In addition, the secondary efficacy outcomes as adjudicated by ICAC (if applicable) will be analyzed using the same Cox PH model as described in section 6.2.5 based on the SAF and on-treatment data scope.

If the sensitivity analyses are much different from the primary analysis, additional analyses may be performed to further investigate the inconsistency.

Concordance of ICAC and investigator reports on the primary efficacy endpoint events will be provided for the combined treatment group.

Sensitivity analyses to address the potential impact of missing data

Although extensive effort will be made to reduce the number of subjects with missing follow-up, it is expected that there will be missing vital status and event information in some subjects. Subjects who are not followed up until the ECOD (consent withdrawal, objection to further data collection, and lost to follow up) before the development of primary efficacy events will be considered missing.

Sensitivity analyses will be performed for the primary efficacy endpoint based on the ITT analysis set and ITT data scope to evaluate the potential impact of missing data on analysis results and robustness of study conclusions.

To evaluate the plausibility of informative censoring, distributions of baseline demographics and other characteristics will be compared between subjects with and without missing data, taking into account treatment and regardless of treatment.

Potential impact of missing data will be evaluated by imputation, where the event process will be imputed in missing follow-up periods (ie. time from last clinical event ascertainment date until ECOD in subjects without a primary efficacy endpoint prior to the ECOD). The robustness of the treatment effect with respect to missing data will be evaluated with a tipping point analysis (see Appendix C for mathematical details). In this analysis, we will:

1. Estimate the hazard at time of loss to follow-up among subjects in ITT analysis set, adjusting for treatment group, stratification factors, and the following baseline covariates:
    - age (<65; ≥65 to <75; ≥75 years)
    - diabetes mellitus (yes, no)
    - prior coronary artery disease (yes, no)
2. Inflate the hazard only in the rivaroxaban group by a set of inflation factors; assuming non-informative censoring in the control group

3. Perform simulations to impute events to the end of the study using standard multiple imputation rules, and compute the hazard ratio and two-sided 95% CI using the primary Cox proportional model
4. Given the study results is statistically significant in favor of rivaroxaban, increase the inflation factor (by repeating steps 2 and 3) until the upper limit of the two-sided 95% CI for the hazard ratio crosses 1.0; this will be the "tipping point"

The tipping point will show how much higher the event risk after drop-out would need to be in the rivaroxaban group so that statistical significance is lost.

In addition, the extent of missing information will be described by the fraction of subjects with missing data and the fraction of unobserved rivaroxaban or rivaroxaban placebo follow-up subject-years.

6.3 Pharmacokinetics/pharmacodynamics

Not applicable

6.4 Safety

6.4.1 Adverse events

Because the safety profile of rivaroxaban has been well established in previous large and extensive trials, this study will collect limited AE data. Adverse events (AEs) will be coded by Medical Dictionary for Regulatory Activities (MedDRA). The version number of MedDRA used for the analyses will be stored in the clinical database. A listing will be provided linking the original investigator terms and the coded terms.

Analyses of reported adverse events will be performed based on the SAF and on-treatment data scope.

In case of uncertainty (e.g., missing or incomplete dates), AEs will be classified as "treatment emergent" (TE) following the worst case approach.

An overall summary of AEs and treatment-emergent (TE) AEs (only considering study medication of rivaroxaban or rivaroxaban placebo) will be generated by treatment group and overall.

Incidences of subjects with treatment emergent adverse events (TEAEs), drug-related and/or serious TEAEs, and TEAEs causing discontinuation of study drug will be summarized by treatment grouped by MedDRA Primary System Organ Class (SOC) and Preferred Term (PT). In addition, the incidence of pre-treatment AEs and AEs during the post study treatment follow up will be tabulated.

Serious adverse events (SAEs), AEs leading to discontinuation and AEs of special safety interest (if applicable) will be listed. The date, relative day (to start of study medication) and phase of the study (pre-treatment, during treatment, post-treatment) will be included.

Further summaries of AEs by maximum intensity and worst outcome will be provided, consistent with Bayer Global Medical Standards.

Specific to Japan, outcome events (i.e. bleeding, efficacy outcome events) are reported as an (S)AEs as required by PMDA, thus (TE)AEs and SAEs will be further presented for Japan only subjects vs. non-Japan subjects.

6.4.2 Primary safety variable

The primary safety variable is the time from randomization to the major bleeding events according to the thrombolysis in myocardial infarction (TIMI) classification, as defined in the ICAC charter.

6.4.3 Secondary safety variables

The secondary safety variables are:

- the time from randomization to the major bleeding events according to the International Society on Thrombosis and Haemostasis (ISTH) classification
- the time from randomization to the type 3b and above bleeding events according to the Bleeding Academic Research Consortium (BARC) classification

Bleeding definitions can be found in the ICAC charter.

6.4.4 Other safety variables

Other safety variables include vital signs (systolic and diastolic blood pressure, pulse rate).

6.4.5 Analysis of safety variables

The analysis of the primary and secondary safety variables will be based on the SAF and on-treatment data scope.

Time to the first occurrence of the primary safety endpoint (i.e., TIMI major bleeding) will be compared using a Cox proportional hazards model stratified by type of procedure and use of clopidogrel (per IxRS assignment) with treatment group as a covariate. A plot of cumulative event rate derived by Kaplan-Meier estimate will be provided to show event rate and treatment effect by time.

The secondary safety outcome variables will be analyzed similarly.

As supportive analyses, the primary safety variable will be analyzed as described above based on the SAF and ITT data scope as well as overall study duration including post-study treatment follow-up. In addition, the primary safety variable will be analyzed according to the actual qualifying revascularization procedure (section 6.2.9) and in subgroups as described in section 6.2.4. Number of subjects with multiple TIMI major bleedings will also be summarized in frequency table.

As exploratory analyses, landmark analysis similar to those as described in section 6.2.8 will also be performed for the primary safety variable.

Additionally number of patients with bleeding leading to permanent drug discontinuation will be summarized by bleeding sites.

Concordance of ICAC and investigator reports on the TIMI major bleeding events will be provided for the combined treatment group.

Other safety variables will be summarized descriptively.

Any pregnancy occurring in a study subject during the subject's participation in this study will be displayed.

6.5 Other procedures and variables

The other procedures and variables include:

- Health care resource utilization data
- PAD symptom status

For these variables, additional analyses other than those specified in sections 6.2.7 and 6.2.8 may be performed and reported separately.

6.6 Benefit/Risk Assessment

The benefit-risk analyses are structured to allow an integrated evaluation of the key benefits and risks in the study. They are complementary to the efficacy and safety analyses described previously in this document and not intended for hypothesis testing. These analyses will be performed in patient populations with the same follow up. Details of these analyses will be described in a separate document (supplemental statistical analysis plan for benefit-risk).

The benefit-risk evaluation will be based on the comparison of the time-to-first-event rates (rivaroxaban added to ASA vs. ASA alone), for events intended to be prevented (benefits) and events that may be caused (risks). Individual outcome measures balanced and weighed by clinical significance and severity will be compared to evaluate the trade-off between prevention of thrombotic vascular events versus harm (i.e. bleeding). These outcome measures include the individual components of the primary efficacy outcome, risk measurements include the hemorrhagic events of the efficacy endpoint and bleedings according to TIMI classification. To have a comprehensive benefit-risk evaluation, several quantification methods will be used.

Results of the above analysis do not preclude additional benefit/risk assessment in other endpoints. The overall benefit-risk profile of the study drug will be interpreted in consideration of the totality of the data.

7. Document history and changes in the planned statistical analysis

Version	Date	Action
Draft SAP submitted to FDA	12 June 2015	
Version 1.0	7 April 2016	Updates based on protocol amendment #4 and FDA feedback on planned sensitivity analyses to assess the impact of missing data
Version 2.0	14 May 2018	• Order of secondary efficacy endpoints were changed according to Global Integrated Clinical Study Protocol version 3.0 • Efficacy cut-off date and censoring rules for efficacy endpoints were modified in

Version	Date	Action
		section 4.5.1, 4.5.3 and Appendix A • Added a few more subgroup variables in section 6.2.4 • Added more exploratory analyses (e.g. MACE/MALE endpoints, landmark analysis for primary efficacy endpoint) in section 6.2.8 • Added more sensitivity analyses of primary and secondary efficacy endpoints in section 6.2.10 • Added AEs analyses for Japan vs. non-Japan patients in section 6.4.1, and supportive analyses in section 6.4.5. • Updated benefit/risk analysis in section 6.6 • Added Appendix B for the definition of regions • Added Appendix C to describe the mathematical details of the tipping point analysis
Version 3.0	24 July 2019	None of the edits in this SAP version is considered to change the primary efficacy analysis and other analyses as described in the SAP version 2.0, but includes further clarifications and additional analyses. Editorial, administrative, and typographical corrections were made that do not affect the overall SAP. These changes are not described in this section. The following changes are introduced in SAP version 3.0: • Added information on imputation rules for the missing or incomplete post-randomization event dates in section 4.3 • Added information on derivation of the first dose and last dose date of study treatment in section 4.5.1. • Added analysis in data scopes with overall study duration for sensitivity analysis in section 4.5.2 • Added information on censoring rules for efficacy endpoints in section 4.5.3 and

Version	Date	Action
		Appendix A • Added analysis on SAF with on-treatment data scope for secondary efficacy endpoints, subgroup variables, and changed sensitivity analysis for primary efficacy endpoints with on-treatment data scope from ITT to SAF in Table 1 • Updated some demographic variables in section 6.1.2 • Updated other efficacy variables in section 6.2.3 • Updated some subgroup variables in section 6.2.4 • Updated SAS code to display both one-sided and two-sided p values in section 6.2.5 • Updated exploratory analysis with detailed statistical model information in the multiple occurrences of the primary efficacy endpoints analysis and references in section 6.2.8 • Updated exploratory analysis in the subgroup variables in section 6.2.8 • Added additional landmark analysis on the time period from randomization to 6-month, 6-month to 1 year and 1-year to end of treatment phase in section 6.2.8 • Added likelihood ratio test analysis to test for interaction terms in the subgroup analysis in section 6.2.9 • Added sensitivity analyses on individual components of primary efficacy endpoints on SAF and on-treatment data scope in section 6.2.10 • Updated sensitivity analyses on the missing data tipping point analysis by including the additional baseline covariates in the Cox model in section 6.2.10 • Removed European quality of life 5 dimensions questionnaire and walking impairment questionnaire variables in section 6.5. Those variables were

Version	Date	Action
		mentioned in section 6.2.3 • Updated Efficacy cut-off date, timelines, and censoring variables in Appendix A • Added Appendix D for the detailed information on imputation rules for missing dose date • Added Appendix E for the definition on the components of the primary efficacy outcome by the investigators

8. References

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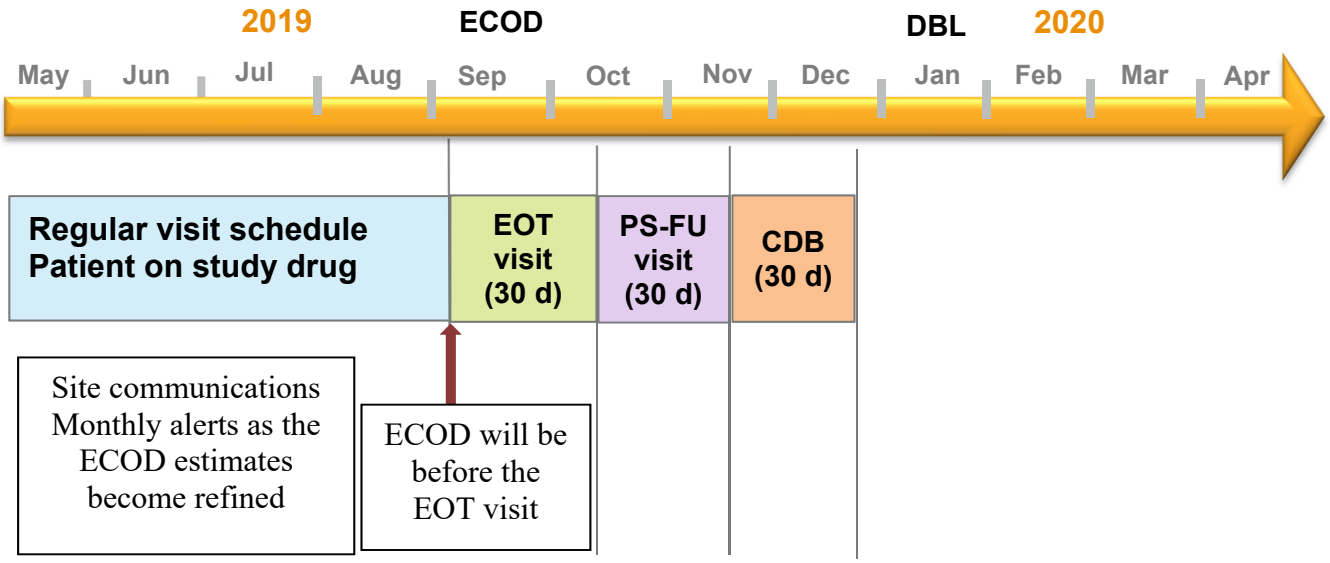
Appendix A: Study Closeout Procedure and Variables used for Censoring



Note: The dates and timeline shown are for illustration purpose only. ECOD= Efficacy cut-off date, EOT Visit=end of treatment visit, PS-FU Visit=Post-study treatment follow-up visit (phone call), DBL=database lock

The executive committee will monitor the accrual of the number of primary events, and when appropriate predict and define an ECOD at which time the pre-defined target number of events for the primary composite endpoint are expected to have occurred. All randomized patients should return for their End of Treatment (EOT) visit after the ECOD.

Events that occur after the ECOD will also be collected and adjudicated. These events will be included in sensitivity analyses but not the primary analysis.

For the implementation of the censoring rules below variables are defined to distinguish between a patient's last contact with information relating to clinical events versus CV-death / all-cause mortality.

- Date of objection to further data collection

  This date will be given only for those subjects who expressed objection to further data collection after withdrawal of informed consent.

- Last clinical event ascertainment date

  The latest date from regular or unscheduled post-randomization visits or contacts with assessment of clinical events or latest adjudicated clinical event start date.

- Date of last contact alive

  The date of the last documented contact with the subject or a third party (including data on subject survival status) derived from the maximum (last clinical event ascertainment date, SAEs date, vital status date, consent withdrawn date or date of objection to further data collection). The resulting maximum date is capped by the death date if the patient died or by the date of clean database. In addition, the date of last contact alive will be the day before the death date, if available, for subjects who die.

Appendix B: Definition of Regions

Countries will be assigned to regions as shown in Table 2 below. If additional countries participate in the trial, their assignment to a region will be specified in the table/listing/figure specification document before unblinding.

Table 2 Classification of Countries to Regions

Region	Countries
North America	Canada, USA
Western Europe	Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, United Kingdom
Eastern Europe	Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, Ukraine
Asia Pacific	China, Japan, South Korea, Taiwan, Thailand
South America	Argentina, Brazil

Appendix C: Mathematical Details of the Proposed Tipping Point Analysis

The robustness of the treatment effect with respect to missing data will be evaluated with a tipping point analysis for the primary efficacy variable. A methodology similar to pattern-mixture-models will be employed, where a Weibull survival model will be fitted to impute outcome for subjects who are lost-to-follow-up (or withdrawn consent with no further information) (Little 2016).

1. Estimate the hazard at time of loss to follow-up, adjusting for treatment group, covariates and stratification factors

   a. The log survival time w=log(t) is modeled using SAS LIFEREG procedure by fitting a Weibull distribution to all subjects, adjusting for treatment group, covariates and stratification factors. The survival function has the form

   $$S_0(w) = \exp\left(-\exp\left(\frac{w-\mu}{\sigma}\right)\right),$$

   where μ (differs for treatment, covariates, and stratum) and σ (scale) are estimated from the SAS output.

   b. Re-parametrize the Weibull distribution with survival function

   $$S(t) = exp(-(t/\lambda)^{\beta}),$$

   where λ is the scale parameter and β is the shape parameter. Obtain the estimates of λ and β as

   $$\lambda = exp(\mu)$$

   $$\beta = 1/\sigma.$$

   c. Obtain the observed hazard rate for individual subjects using the hazard function

   $$h(t|\lambda, \beta) = (\beta/\lambda)(t/\lambda)^{\beta-1}.$$

2. Inflate the hazard only in the rivaroxaban group by a set of inflation factors; assuming non-informative censoring in the control group

Let *k* be the inflation factor, the inflated hazard rate in the rivaroxaban group is

$$h^*(t|\lambda, \beta) = k\times(\beta/\lambda)\,(t/\lambda)^{\beta-1}$$

and the new scale parameter is

$$\lambda^* = \lambda/(k^{1/\beta})$$

by solving λ^* from $k\times(\beta/\lambda)\,(t/\lambda)^{\beta-1} = (\beta/\lambda^*)\,(t/\lambda^*)^{\beta-1}$, while fixing the shape parameter β.

The hazard rate in the control group remains unchanged.

3. Perform simulations to impute events to the end of the study using standard multiple imputation rules (Rubin 1987), and compute the hazard ratio and two-sided 95% CI using the primary Cox proportional model

For subjects who are lost-to-follow up (or withdrawn consent with no further information), and who did not experience a primary efficacy endpoint prior to the ECOD, random variables will be simulated using the conditional time to event distribution after the last contact date (*LC*) (defined as earlier date of last clinical event ascertainment date, date of the objection to further data collection) given that no event was observed before.

Let *x* be the time from the last contact date (*LC*) to the event date, the conditional probability of having an event given no event observed before *LC* is

$$y = \Pr(t \le x + LC \mid t > LC) = 1 - \Pr(t > x + LC \mid t > LC)$$
$$= 1 - \frac{\Pr(t > x + LC)}{P(t > LC)} = 1 - \frac{S(x + LC)}{S(LC)}.$$

Using the estimated scale parameter λ^* and shape parameter β from Weibull distribution in step 2, the above becomes

$$y = 1 - \exp(-((x+LC)/\lambda^*)^{\beta}) / \exp(-(LC/\lambda^*)^{\beta}),$$
$$\Leftrightarrow \log(1-y) = -((x+LC)/\lambda^*)^{\beta} + (LC/\lambda^*)^{\beta}$$
$$\Leftrightarrow x = \lambda^*((LC/\lambda^*)^{\beta} - \log(1-y))^{1/\beta} - LC.$$

If *y* is generated as a random variable with uniform distribution between 0 and 1, the random variable *x* can be generated using the inverse transformation technique from the formula above.

If this randomly generated variable has a value less than the elapsed time between the last contact date and the efficacy cut of date, the subject will be counted as having observed an event at the last contact date plus the random variable. Otherwise, the subject is re-adjusted to be censored at the ECOD.

These imputed events will be added to the observed events in the study for both treatments and the primary efficacy variable will be re-analyzed. This process will be repeated 1000 times. The hazard ratio with 95% CI will be estimated for each imputed data set and then combined using standard multiple imputation combining rules.

4. Given the study results is statistically significant in favor of rivaroxaban, increase the inflation factor (by repeating steps 2 and 3) until the upper limit of the two-sided 95% CI for the hazard ratio crosses 1.0; this will be the "tipping point".

Reference:

Little, RL, Wang, J., Sun, X. et. al. The treatment of missing data in a large cardiovascular clinical outcomes study. Clinical Trials, 2016 vol. 13 no. 3 344-351

Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley, 1987

Appendix D: Imputation Rules for Missing Dose Date

First dose date is missing or incomplete	Action
Only day of first dose date is missing	Impute the first dose date as maximum (date of randomization+1 day, 01.month.year)
Month and day of first dose date is missing	Impute the first dose date as randomization + 1 day.
First dose date is complete missing but last dose date is available	Impute the first dose date as randomization + 1 day.
First dose date and last dose date is missing	The patient never took the study medicine
Last dose date is missing or incomplete	**Action**
Only day of last dose date is missing	• Impute the last dose date using last day of the month • Derive last dose date as minimum of (the date of last contact, imputed last dose date, the date of death, or the maximum of (ECOD, EOT visit date)) but no earlier than the date of first dose.
Month and day of last dose date is missing	• Impute the last dose date using last day of the year • Derive last dose date as minimum of (the date of last contact, imputed last dose date, the date of death, or the maximum of (ECOD, EOT visit date)) but no earlier than the date of first dose.
Last dose date is complete missing but first dose date is available	Impute last dose date as minimum of (the date of last contact, the date of death, or the maximum of (ECOD, EOT visit date)) but no earlier than the date of first dose.

Appendix E: Components of the Primary Efficacy Outcome by the Investigators

- CV death: Either any death in the main category "Cardiovascular cause" or within the "Other cause" main category including any death indicated by the investigator that the cause was unknown.
- MI: coronary ischemic event diagnosis in
    - Non-stemi
    - Stemi
- Ischemia stroke: stroke type in
    - Primary ischemic stroke
    - Primary ischemic stroke with hemorrhagic conversion
    - Unknown stroke type
- Acute limb ischemia
- Amputation: reason for amputation in primary acute limb ischemia and primary vascular disease progression with site of leg in
    - Above the knee
    - Below the knee, ankle disarticulation
    - Below the knee, transtibial