Document Type:	Study Protocol
Official Title:	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
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Cover page of the integrated protocol

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

This protocol version is an integration of the following documents / sections:

- **Original protocol,** Version 1.0, dated 23 MAR 2015
- **Amendment 4** (global amendment described in Section 15.1) forming integrated protocol Version 2.0, dated 10 FEB 2016
- **Amendment 5** (global amendment described in Section 15.2) forming integrated protocol Version 3.0, dated 21 MAR 2017

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol:

- **Local Amendment 1**, valid for Japan, dated 28 APR 2015
- **Local Amendment 2**, valid for United Kingdom (UK), dated 25 AUG 2015
- **Local Amendment 3**, valid for Czech Republic, dated 15 SEP 2015

1. Title page - amended

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

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

Test drug:	BAY 59-7939 / Rivaroxaban / Xarelto		
Clinical study phase:	3	Date:	21 MAR 2017
Registration:	EudraCT: 2014-005569-58	Version no.:	3.0
Sponsor's study no.:	BAY 59-7939 / 17454		
Sponsor:	Non-US territory: Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA[1]		
Sponsor's study medical expert[2]:	PPD Bayer HealthCare Pharmaceuticals Inc. 100 Bayer Blvd, PO Box 915 Whippany, NJ 07981-0915; United States Phone No. PPD		

The study will be conducted in compliance with the protocol, ICH-GCP, and any applicable regulatory requirements.

Rivaroxaban (BAY-59-7939, JNJ-39039039) is being co-developed under a collaboration and license agreement between Bayer HealthCare AG (BHC) and Ortho McNeil Pharmaceuticals, Inc. (OMP) dated 01 Oct 2005. As determined by the parties, both BHC and Janssen Pharmaceuticals Inc. (successor in interest to OMP) may use affiliated corporate entities to conduct this clinical study. With regard to Janssen Pharmaceuticals Inc., such affiliates may include Janssen Research & Development, LLC (formerly Johnson & Johnson Pharmaceutical Research & Development LLC), Janssen Scientific Affairs, LLC, and Janssen-Cilag International N.V (Corporation). The term "sponsor" or "designee" is used to represent these various legal entities that have been identified to perform various clinical study services; the actual sponsor or designee is identified on the Contact Information page that accompanies this protocol.

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1 Updated sponsor information via Protocol Amendment 5 (change no. 1).

2 Updated name and contact details for Sponsor's medical expert with Protocol Amendment 4 (change no. 1).

Signature of the Sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD

Role: PPD

Date: 22 March 2017

Signature:

Signature of the principal investigator for the study

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: Signature:

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

2. Synopsis - amended

Title	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
Short title / Acronym	**V**ascular **O**utcomes stud**Y** of **A**SA alon**G** with rivaroxaban in **E**ndovascular or surgical limb **R**evascularization for peripheral artery disease (PAD) VOYAGER PAD
Secondary IDs	IMPACT No. 17454 / EUDRACT No.: 2014-005569-58
Clinical study phase	Phase 3
Study objective(s)	Primary efficacy objective: • to evaluate whether rivaroxaban added to acetylsalicylic acid (ASA) is superior to ASA alone in reducing the risk of major thrombotic vascular events (defined as myocardial infarction (MI), ischemic stroke, cardiovascular (CV) death, acute limb ischemia (ALI), and major amputation of a vascular etiology) in symptomatic PAD patients undergoing lower extremity revascularization procedure. Secondary efficacy objectives: • 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);[3] • 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[4]; Primary safety objective: • to evaluate the overall safety and tolerability of rivaroxaban added to ASA compared to ASA alone.

[3] This objective was revised with Protocol Amendment 4 (change no. 8) and Protocol Amendment 5 (change no. 2).

Test drugs	Xarelto®
Name of active ingredient	Rivaroxaban
Dose(s)	2.5 mg twice daily (bid)
Route of administration	oral
Duration of treatment	A mean treatment duration of approximately 30 months and a maximum treatment duration of up to approximately 42 months is estimated. This study will be event-driven, thus all patients will be treated (or followed-up in the case of permanent discontinuation of study medication) until the required primary efficacy outcomes have occurred.
Reference drug(s)	
Name of active ingredient	Rivaroxaban-matching placebo
Dose(s)	matching placebo bid
Route of administration	oral
Duration of treatment	Same as for test drug (see above).
Background treatment	All study patients will receive treatment with open label ASA 100 mg orally once daily (od) during the entire course of the study; additional treatment with clopidogrel may be administered for a planned duration of up to 30 days after the qualifying revascularization procedure (or up to 6 months for complex procedures or devices in the investigator's opinion that require longer use); it is strongly recommended that any course of clopidogrel is kept to the minimum necessary in accordance with local standard of care and international practice guidelines (typically 30 days, or up to 60 days for some drug-coated products or devices)(*see section 8.1 for further guidance on clopidogrel*). [5]
Indication	Symptomatic PAD
Diagnosis and main criteria for inclusion/exclusion[6]	Main inclusion criteria are: • age ≥ 50, • documented moderate to severe symptomatic lower extremity atherosclerotic peripheral artery disease as evidenced by ALL of the following: a. clinically, by functional limitations in walking activity, ischemic rest pain, or ischemic ulceration, b. anatomically, by imaging evidence of peripheral artery disease distal to the external iliac artery in the index leg within 12 months prior to or at the time of the qualifying revascularization, AND c. hemodynamically in either leg (within 12 months prior to, or at the time of, the qualifying revascularization) by: ▪ an ABI ≤ 0.80 or TBI ≤ 0.60 for patients without a prior history of limb revascularization,

4 The last 2 secondary objectives were revised with Protocol Amendment 4 (change no. 17).
5 This section was modified with Protocol Amendment 5 (change no. 3).
6 Modifications to the inclusion and exclusion criteria were made with Protocol Amendment 4 (change no. 4, 5, 7, 15, 17 and 20a, b, c)

	OR ▪ an ABI ≤ 0.85 or TBI ≤ 0.65 for patients with a prior history of limb revascularization. Main exclusion criteria are: • patients undergoing revascularization for asymptomatic PAD or mild claudication without functional limitation of the index leg,[7] • patients undergoing revascularization of the index leg to treat an asymptomatic or minimally symptomatic restenosis of a bypass graft or target lesion restenosis, • prior revascularization on the index leg within 10 days of the qualifying revascularization, • Planned dual anti-platelet therapy (DAPT) use for the qualifying revascularization procedure of clopidogrel in addition to ASA for >6 month after the qualifying revascularization procedure; it is strongly recommended that any course of clopidogrel is kept to the minimum necessary in accordance with local standard of care and international practice guidelines (typically 30 days, or up to 60 days for some drug-coated products or devices) and is only allowed for up to 6 months for complex procedures or devices in the investigator's opinion that require longer use; *see section 8.1 for further guidance on clopidogrel* [8], [9] • Planned use of any additional antiplatelet agent other than clopidogrel and ASA after the qualifying revascularization procedure.[10]
Study design	International, multicenter, randomized, double-blind, placebo-controlled, event-driven phase 3 study.
Methodology[11]	Patients meeting the eligibility criteria will be treated with study ASA and randomly allocated by an interactive voice/web response system (IxRS) in a ratio of 1:1 to treatment with either rivaroxaban or matching placebo. 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), and treatments will be balanced within a country for each stratum by block randomization. Randomization and study treatment will commence as soon as possible but no later than 10 days after the qualifying revascularization. The first study visit is a screening visit to be performed within 30 days prior to or no more than 10 days after the qualifying revascularization. The second study visit is the randomization visit, which should be performed as soon as possible (but no later than 10 days) after the qualifying revascularization. The first dose of study drug should be taken at the randomization visit. The screening and randomization visits can be combined into one visit if all tests required for the assessment of all eligibility criteria are available and

[7] This bullet point was corrected with Protocol Amendment 5 as requested by the Note to File for Protocol Amendment 4 (change no. 7).
[8] Exclusion criterion 7 revised with Protocol Amendment 4 (change no. 17).
[9] Exclusion criteria concerning DAPT were modified via Protocol Amendment 5 (change no. 3).
[10] Exclusion criterion modified via Protocol Amendment 5 (change no. 7).
[11] Text modified with Protocol Amendment 4 (changes no. 2, 3 and 17).

	randomization and dosing can be performed within close proximity. Subsequent on-site study visits will be completed at 1, 3, 6, and 12 months (Visits 1-4) after randomization, and then every 6 months after Visit 4 until end of treatment (EOT visit). Due to the event-driven study design, no firm treatment duration can be stipulated for an individual patient. However, the mean treatment duration is estimated to be approximately 30 months and the maximum treatment period for an individual patient to be approximately 42 months. The EOT visit will be performed as soon as possible after the announcement of study end or upon individual premature termination of the study. **All efforts must be taken to engage patients to continue to be followed until the end of the trial preferably by regular site visits, or at least by phone contacts**. Finally, a post-study treatment follow-up visit will be performed by phone in all patients one month after the EOT visit. Patients will be assessed at each study visit for the occurrence of study efficacy outcome events, bleeding events, and adverse events (AEs). The time period for reporting of all these events will begin with informed consent and will end with the post-study treatment follow-up visit. Patients who experience a study efficacy outcome event or bleeding event while enrolled in the trial should continue study treatment, if medically justifiable. All patients who have discontinued study drug treatment prematurely will be followed according to the regular visit schedule, and ascertainment of all events including, but not limited to study efficacy outcome events, bleeding events, and vital status (alive or deceased) must be assessed in these patients until the end of the study via clinic visits or telephone contacts, as outlined in the protocol. Patients who withdraw consent will continue to be monitored for vital status and study efficacy outcome events as allowable per country regulations.
Type of control	Matching placebo
Trial Committees	An Executive Committee (EC) will contribute to the protocol development, analysis plans, and publications and oversee the conduct of the trial. An International Steering Committee (ISC) will provide scientific input and oversight of countries and sites. The study efficacy outcome and bleeding events will be adjudicated by an Independent Central Adjudication Committee (ICAC). Safety data will be continuously assessed by an Independent Data Monitoring Committee (IDMC).
Number of subjects	Approximately 6,500 patients (i.e., 3,250 per treatment group) will be enrolled in order to attain 1,015 patients that experience a positively-adjudicated primary efficacy outcome event. The number of patients enrolled may be adjusted based on a blinded review of the observed overall event rate of confirmed and projected primary outcome events during the study.

Primary and secondary variable(s)	The primary efficacy outcome variable will be a composite endpoint consisting of the time from randomization to the first occurrence of any of the following major thrombotic vascular events: MI, ischemic stroke, CV death, ALI, and major amputation due to a vascular etiology. The secondary efficacy variables of the study will be: • 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 revascularizations that were not planned or considered as part of the initial treatment plan at the time of randomization);[12] • 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 venous thromboembolic (VTE) events; The primary safety outcome will be major bleeding events according to the Thrombolysis in Myocardial Infarction (TIMI) classification.
Plan for statistical analysis	The primary efficacy analyses will be based on the intent-to-treat (ITT) population using adjudicated results. The rivaroxaban plus study ASA group will be compared to the placebo plus study ASA group using a stratified log rank test. Kaplan-Meier curves for the cumulative incidence risk and cumulative incidence functions will be provided to evaluate the timing of event occurrence. Relative risk reduction will be estimated with the stratified Cox proportional hazards model. Secondary efficacy outcomes will be analyzed using similar methods as for the primary efficacy analysis. Testing will be performed in an hierarchical order. The analysis of the primary safety outcome will be similar to those described for the primary efficacy outcome. There will be one formal interim analysis to assess efficacy and allow for stoppage if overwhelming superiority is detected ($p<0.001$), which will occur when approximately 67% of the planned primary efficacy outcomes have accrued.

[12] Text modified with Protocol Amendment 4 (change no. 8) and Protocol Amendment 5 (see change no 2).

Anticipated total study duration and study duration per patient	Total study duration:	~42 months
	Enrollment period:	~18 months
	Treatment duration for last patient randomized:	~24 months
	Mean treatment duration per patient:	~30 months
	Maximum treatment duration per patient:	~42 months
	The study will be event-driven and these timelines may vary depending on the enrollment rate and event rate in the study.	

Table of contents

Table of tables

Table of figures

List of abbreviations - amended

Adapted via Amendment 4

ABI	Ankle-Brachial Index
ACCF	American College of Cardiology Foundation
ACCP	American College of Chest Physicians
ACS	Acute coronary syndrome
AE(s)	Adverse event(s)
AF	Atrial fibrillation
AHA	American Heart Association
ALI	Acute limb ischemia
ALT	Alanine transaminase
APCC	Activated Prothrombin Complex Concentrate
ARO	Academic Research Organization
ASA	Acetylic salicylic acid
AST	Alanine Aminotransferase
ATLAS ACS	Anti-Xa Therapy to Lower cardiovascular events in Addition to standard therapy in Subjects with Acute Coronary Syndrome trial
BARC	Bleeding Academic Research Consortium
BHC	Bayer HealthCare
bid	Bis in die (twice daily)
BMI	Body Mass Index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (trial)
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (trial)
CI	Confidence interval
CLI	Critical limb ischemia
COMPASS	Cardiovascular OutcoMes for People using Anticoagulation StrategieS (a randomized controlled trial of rivaroxaban for the prevention of major cardiovascular events in patients with coronary or peripheral artery disease)
CRF/eCRF	Case report form/electronic CRF
CRO	Contract Research Organization
CT	Computed tomography
CV	Cardiovascular
CVD	Cerebral Vascular Disease
CYP2C19	Cytochrome P450 isoenzyme 2C19
CYP3A4	Cytochrome P450 isoenzyme 3A4
DAPT	Dual anti-platelet therapy
DVT	Deep vein thrombosis
EC	Executive Committee
ECG	Electrocardiogram
EDC	Electronic Data Capturing
eGFR	estimated glomerular filtration rate

EOT	End of treatment
EQ-5D	European Quality of Life-5 Dimensions questionnaire
ESC	European Society of Cardiology
EU	European Union
FDA	Food and Drug Administration
FXa	Clotting factor Xa
GCL	Global Clinical Leader
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDL	High density lipoprotein
HDPE	High-density polyethylene
HbA1c	Glycosylated hemoglobin
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IB	Investigator's brochure
ICAC	Independent Central Adjudication Committee
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ISC	International Steering Committee
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent to treat
IxRS	Interactive web/voice response system
kg	kilogram
LDL	Low density lipoprotein
LMWH	Low molecular weight heparin
MDRD	Modification of Diet in Renal Disease (formula)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial infarction
mL	Milliliter
mmol	Millimole
MRI	Magnetic resonance imaging
NOAC	Non vitamin K antagonist oral anticoagulant
NSAID	Non-steroid anti-inflammatory drug
od	Once a day
OR	Odds ratio
P2Y12	P2Y12 receptor antagonist (antiplatelet agent)
PAD	Peripheral artery disease
PBRER	Periodic benefit-risk evaluation report
PCI	Percutaneous coronary intervention

PE	Pulmonary embolism
P-gp	P-glycoprotein
PS-FU	Post-study treatment follow-up visit
PSUR	Periodic safety update report
PV	Pharmacovigilance
QoL	Quality of life
REACH	Reduction of Atherothrombosis for Continued Health
RR	Relative risk
RxV	Randomization visit
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SAS	Statistical analysis system
ScV	Screening visit
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SUSAR	Suspected unexpected serious adverse reaction
TBI	Toe-Brachial Index
TIA	Transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction (study group)
TOSCA	Tools for syntactic corpus analysis
TRA2P-TIMI	The Trial to Assess the Effects of vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis
UFH	Unfractionated heparin
UK	United Kingdom
US/USA	United States of America
VOYAGER PAD	Vascular Outcomes studY of ASA alonG with rivaroxaban in Endovascular or surgical limb Revascularization for peripheral artery disease (PAD)
VKA	Vitamin K Antagonist
VTE	Venous thromboembolism
WAVE	Warfarin and Antiplatelet Vascular Evaluation trial
WIQ	Walking Impairment Questionnaire
WHO	World Health Organization

Definitions of medical terms - amended

Dropout	A patient who discontinues study participation prematurely for any reason, if the patient has already been randomized.
Endovascular procedure[13]	Refers to **c**atheter-based and hybrid procedures (those procedures involving aspects of both endovascular and surgical revascularizations) for PAD.
Index leg[14]	Refers to the leg receiving the qualifying revascularization for randomization into this trial.
Qualifying revascularization[15]	Refers to the procedure by which the patient qualifies for the study.
Screening failure	A patient who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before randomization.
Study ASA	Refers to the background treatment with ASA 100 mg od.
Study medication	Refers to either rivaroxaban or placebo.
Successful procedure	Refers to qualifying revascularization (regardless of type of procedure that is considered: 1) a technical success with no immediate plan for re-intervention and per the investigator's discretion, the patient can safely be placed on an anticoagulant at the time of randomization and 2) has demonstrated graft or vascular patency prior to the time of randomization.
Surgical procedure[16]	Refers to open surgical procedure in the lower extremity for PAD. This can include a variety of procedures, bypass conduit materials, and extra-anatomic operations.

[13] Definition revised with Protocol Amendment 4 (change nos. 4 and 17) and Protocol Amendment 5 (see change no. 4).
[14] Definition revised with Protocol Amendment 4 (change no. 7).
[15] Definition revised with Protocol Amendment 4 (change no. 6).
[16] Definition revised with Protocol Amendment 4 (change no. 4) and Protocol Amendment 5 (see change no. 4).

3. Introduction

3.1 Background - amended

Disease characteristics

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 in the coronary circulation [Becker et al. 2011].

Most recent estimates suggest that PAD has now reached pandemic proportion with more than 200 million people living with PAD in 2010, over 40 million in Europe and over 14 million in North and South America. While the condition is generally uncommon in patients younger than 40 years of age, it affects one in 10 individuals aged 70 years or older and one in 6 individuals aged 80 years or older [Fowkes et al. 2013]. In the United States alone, more than 8.5 million individuals are affected by this condition [Go et al. 2014].

Cardiovascular risks associated with PAD

It is now well established that symptoms, severity, and acuteness of PAD are major determinants of subsequent risk of cardiovascular (CV) events and mortality. Independent of symptoms, patients diagnosed with PAD are at an increased risk of subsequent myocardial infarction (MI) and stroke, and are 6 times more likely to die within 10 years than those without PAD [Criqui et al. 1992, Morris et al. 2014].

In the multinational, prospective Reduction of Atherothrombosis for Continued Health (REACH) registry, among the 53,211 symptomatic individuals with established coronary artery disease (CAD), cerebral vascular disease (CVD), or PAD, stable patients with PAD had a numerically higher risk of vascular death, MI, or stroke compared with stable patients with CAD at 1 year (5.4% vs. 4.5%) and at 3 years (14.8% vs. 11.6%) [Abola et al. 2012]. Patients with severe PAD requiring amputations are at even higher risk of CV complications [Abola et al. 2012, Jones et al. 2013]. Similarly, PAD patients requiring surgical revascularizations are at increased risk of CV complications, especially in the first year following the procedure. Patients treated surgically typically have more severe limb symptoms such as severe claudication, ischemic rest pain, and ischemic ulceration that has not responded to endovascular revascularizations [Moxey et al. 2011]. This is in addition to increased risk of perioperative MI and CV events often associated with vascular surgeries [Fleisher et al. 2014, Kristensen et al. 2014]. Even among the less invasive endovascular procedures, in-hospital CV complications and mortality remain high [Vogel et al. 2011].

Ischemic limb risks associated with PAD

The most common initial symptom from underlying progressive atherosclerotic occlusion of the peripheral vasculature is leg pain on exertion or intermittent claudication. In patients with more severe disease, critical limb ischemia (CLI) can present with pain at rest, ulceration, tissue loss, and/or non-healing ulcers and gangrene. The incidence of CLI is estimated to be

approximately 500 to 1000 new cases per year per million people, with significant growth expected due to aging of the population and the increased prevalence of diabetes [Fowkes et al. 2013, Tendera et al. 2011]. Patients diagnosed with CLI are at increased risk of major amputation, impaired physical function, and a marked reduction in the quality of life [Abola et al. 2012, Mangiafico and Mangiafico 2011]. More acutely, PAD patients may present with acute atherothrombotic occlusions resulting in ALI, a condition marked by a sudden decrease in limb perfusion that threatens the immediate viability of the affected limb.

Historically, 1-year mortality among CLI patients is approximately 10%, with loss of limb around 20% without revascularization [Conte et al. 2009]. However, even with revascularization, ALI and CLI patients remain at risk of subsequent need for amputation and death [de Donato et al. 2006, Goodney et al. 2010]. In a recent analysis that evaluated all admissions for lower extremity thromboembolism (1.76 million cases) resulting either from ALI or acute exacerbation of CLI over a 20-year period in the National Hospital Discharge Survey from 1998 to 2007, while there was notable improvement in outcomes, in-hospital mortality remained high at approximately 6%, with overall in-hospital amputation rate at approximately 7% [Korabathina et al. 2013].

3.2 Drug management of PAD

Use of antiplatelet drugs in PAD

While ASA remains the cornerstone therapy and the most recommended treatment for the secondary prevention of atherothrombotic events, its efficacy has been increasingly questioned [Anderson et al. 2013, Baigent et al. 2009, Berger et al. 2009, Tendera et al. 2011, Wong and White 2011, Wong et al. 2013]. The benefits of clopidogrel compared with ASA, as observed in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial (n=19,185), appeared modest at best in the overall cohort, with an 8.7% relative risk (RR) reduction of composite outcomes of ischemic stroke, MI, or vascular death at 3 year (p=0.043). Interestingly, observed benefits were not consistent across the subgroups of CAD, CVD, and PAD, with the efficacy driven primarily by those PAD patients with a history of MI [CAPRIE-Steering-Committee 1996]. In the subsequent Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial (n=15,603), when clopidogrel was added to ASA, not only were additional benefits not observed in the overall trial, but also benefits were not reproduced in the PAD group [Bhatt et al. 2007, Bhatt et al. 2006, Cacoub et al. 2009]. As a result, clopidogrel use in PAD is largely limited as a single agent, an alternative to ASA, while benefits of dual antiplatelet therapy (DAPT) have not been confirmed, particularly since CHARISMA was a negative trial. Monotherapy of clopidogrel, as a therapeutic option in PAD patients is further complicated by recent revelations about interactions with proton pump inhibitors such as omeprazole or esomeprazole and Cytochrome P450 isoenzyme 2C19 (CYP2C19) polymorphism [Wedemeyer and Blume 2014].

Most recently, in the TRA2°P-TIMI 50 trial, vorapaxar (a novel antiplatelet agent) added to standard of care that included ASA and clopidogrel was associated with an overall 13% RR reduction of composite outcomes of CV death, MI, or stroke, but at a cost of a significant increase in moderate or severe bleeding including intracranial hemorrhage. Among the subset of patients whose qualifying diagnosis was PAD (n=3,787), no significant treatment effect

was observed (Hazard Ratio [HR]: 0.94; 95%-CI: 0.78 to 1.14; p=0.53) while moderate or severe bleeding was significantly increased (HR: 1.62; 95%-CI: 1.21 to 2.18; p=0.001) along with a trend toward increase in intracranial hemorrhage [Bonaca et al. 2013, Morrow et al. 2012]. Interestingly, in a post-hoc exploratory analysis, vorapaxar significantly reduced the risk of limb ischemic events, including hospitalization for acute limb ischemia (2.3% vs. 3.9%; HR: 0.58; 95%-CI: 0.39 to 0.86; p=0.006) and peripheral revascularization (18.4% vs. 22.2%; HR: 0.84; 95%-CI: 0.73 to 0.97; p=0.017). These findings confirmed for the first time that these limb events are likely thrombotic in nature and are potentially modifiable by antithrombotics.

Use of anticoagulants in PAD

Anticoagulants such as warfarin or phenprocoumon alone or in combination with single antiplatelet therapy are effective for the secondary prevention of CV events in patients with CAD, but at the cost of increased bleeding [Anand and Yusuf 2003, Andreotti et al. 2006, Smith et al. 2011].

In the Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial, 2,161 patients with lower extremity and carotid atherosclerotic vascular disease were randomized to antiplatelet therapy alone (ASA) versus antiplatelet therapy plus full dose warfarin (target INR 2.0-3.0) [Anand et al. 2007, WAVE-Investigators 2006]. Over 80 % of the patients had PAD (intermittent claudication plus objective evidence of atherosclerosis). There was no reduction in the primary outcome of CV death, MI, or stroke, or the co-primary outcome which included CV death, MI, Stroke, and severe coronary or limb ischemia requiring urgent intervention. Importantly, there was a 3.5-fold increase in life-threatening bleeding in the warfarin plus ASA group vs. ASA alone, including an excess of intracranial hemorrhage.

Since the potential benefits of vitamin K antagonists (VKA) are often offset by increased bleeding, especially in PAD patients, there is a Grade 1A recommendation in the American College of Chest Physicians 2008 guidelines against the use of anticoagulants in patients with PAD [Sobel and Verhaeghe 2008], and Grade 1B recommendation against its use in PAD [ACCP 2012 guidelines]. Nevertheless, there may be a limited role for VKA in improving outcomes following infra-inguinal bypass surgeries, and the ESC guideline on the management of PAD has a Class IIb recommendation for anticoagulation with VKAs following autologous infrainguinal bypass based on a subgroup analysis of the DUTCH Bypass Oral Anticoagulants or Aspirin trial [Tendera et al. 2011].

Use of revascularization procedures in PAD

Revascularization (either endovascular or surgical) is the treatment of choice in symptomatic patients who are suitable candidates based on clinical history, presentation (e.g., ALI or CLI), and target lesions, as described in the Trans-Atlantic Inter-Society Consensus Document II [Norgren et al. 2007]. With the advent of improved technology and wide-spread accessibility, endovascular therapy is fast becoming the first-line treatment. Given the sequential nature of these procedures, surgical patients today are generally sicker and have more severe disease. Clinical failures in endovascular therapy also remain high because less ideal or high risk patients are offered at least a trial of the less invasive endovascular treatment. In terms of concomitant treatment, the endovascular patients are more likely to be on short term (1 month) empiric DAPT. Because of this potential difference in natural history and therefore

event rates, type of procedure (endovascular or surgical) is proposed as a stratification factor in the present study.

Current treatment guidelines for patients with PAD

At present, due to paucity and low quality of data, the international guidelines of the ACCF/AHA [Anderson et al. 2013] and ESC [Tendera et al. 2011] are divergent regarding their recommendations on optimal antithrombotic therapy in PAD patients, with recommendations often extrapolated from studies from patients with stable CAD or ACS, or from expert opinions. For the primary prevention of cardiovascular events, low-dose ASA (dose range 75 mg/day to 150 mg/day) is the treatment of choice (Class IA), while clopidogrel (75 mg/day) may be an alternative. ACCP 2012 CHEST guidelines recommend single antiplatelet use over DAPT post angioplasty and stent in PAD [Alonso-Coello et al. 2012]. For antithrombotic therapy following interventions, DAPT or ASA plus clopidogrel is often used for a period of one month after infra-inguinal implantation of a bare-metal stent or in case of below-knee bypass with a prosthetic graft. After revascularization procedures, antithrombotic therapy with ASA is generally recommended; a combination with ASA and dipyridamole could be considered after infra-inguinal bypass surgery. VKAs are generally not recommended except in the case of bypass graft surgery when a native conduit is used, but this recommendation is controversial (Class IIb; ESC only).

Summary of currently unmet medical needs

Overall, the currently available treatment options for PAD and evidence-based knowledge on certain patient subsets are suboptimal. Given that the prevalence of conventional cardiovascular risk factors for PAD is increasing, it is likely that the incidence of PAD would grow even more dramatically overtime. The loss of mobility, functional decline, and cardiovascular events, represents a major public health challenge. New and effective treatments are urgently needed to reverse these trends [Biancari 2013, Fowkes et al. 2013].

3.3 Rationale of the study

Given its effectiveness across a broad spectrum of arterial and venous conditions, rivaroxaban has the potential to reduce the burden of a number of thrombosis-related conditions, and to be more effective than prior therapies such as VKAs or aspirin at preventing thrombotic vascular events of a cardiovascular and peripheral vascular nature. Rivaroxaban's mechanism of action, its predictable dose response, its clinically proven anti-ischemic and antithrombotic benefits and its demonstrated beneficial effects on the prevention of stent thrombosis, suggest that it will impact both the traditional coronary outcomes such as CV death, MI, and stroke, and peripheral vascular events such as major amputation and ALI, often associated with early or late procedural failures. Thus, rivaroxaban seems promising for the prevention of coronary atherothrombotic events as well as peripheral vascular events in symptomatic PAD patients who are undergoing peripheral revascularization procedures.

The hypothesis of the present study is that rivaroxaban, when compared to placebo, additional to standard of care therapy using low-dose ASA, has the potential to reduce the incidence of the traditional CV outcomes (i.e., CV death, MI, and stroke) as well as lower limb vascular events, such as ALI and major amputation also in the critical population of symptomatic PAD patients requiring lower extremity revascularization procedures.

3.4 Benefit/risk assessment

Currently available treatment options have been inadequately evaluated and appear insufficient to address the thrombotic complications observed in this distinct population, i.e. PAD patients with a recent lower extremity revascularization procedure. Thus, the potential reduction of major thrombotic events by rivaroxaban is of clinical importance and this research substantially contributes to the knowledge and treatment optimization in these critically ill patients who require lower extremity revascularization procedures.

The choice of standard of care therapy in this study (administered to all study patients) takes into account the current practice and guideline recommendations to allow the use of ASA alone or in transient combination with clopidogrel. In this specific population of patients who have undergone peripheral revascularization procedures, the study mandates the use of ASA in all patients, with the additional clopidogrel for dual antiplatelet therapy permissible (at the discretion of the investigator).

All study efficacy endpoints are clinically meaningful, have been developed and composed on a solid scientific basis, and are established measures in clinical trials. In order to ensure consistent and valid data evaluation, an ICAC will review and adjudicate all potential study endpoints at regular intervals.

Inherently, the prevailing risk on treatment with rivaroxaban is bleeding, which is a recognized complication shared by all anticoagulants. However, patients enrolled in the present study will be closely monitored for the occurrence of bleeding events including peri-procedural bleedings. An IDMC will regularly evaluate for any imbalances between groups with a focus on peri-procedural bleedings.

The safety profile of rivaroxaban is based on an extensive database of safety information collected in a substantial clinical development program, which has enrolled as of Sep 2015 more than 108,000 subjects have been enrolled in interventional clinical trials (completed and ongoing Phase I, Phase II, Phase III and Phase IV) including more than 60,000 subjects treated with rivaroxaban. In addition, the steadily amassing post-marketing data summarized in numerous Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Reports (PBRERs), corresponding to an estimated cumulative patient exposure of 3.7 million patient years, provides further reassurance about rivaroxaban benefit-risk balance in the real-life setting. In conclusion, no undue safety risks are expected from the interventional drug treatment with rivaroxaban in the present study. Further details can be found in the latest available version of the investigator's brochure, which contains comprehensive information on the study drug.[17]

Overall, it is believed that the potential benefits for both participating patients and society clearly outweigh the potential harm that could arise from participation in this study. Complementary to the ongoing COMPASS study of over 21,000 patients with a history of CAD or PAD, in which outcomes of treatment with rivaroxaban 5 mg bid vs rivaroxaban 2.5 mg bid and ASA 100 mg od vs aspirin 100 mg od in stable PAD patients are currently being investigated, the present VOYAGER study is expected to help gain deeper insight into

[17] Sentence was added with Protocol Amendment 4 (change no. 16).

the natural history of PAD and help to optimize treatment in symptomatic PAD patients undergoing lower extremity revascularization procedures.

4. Study objectives - amended

The primary efficacy objective of the study 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 with a recent lower extremity revascularization procedure.

The primary safety objective of the study is:

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

The secondary efficacy objectives of the study 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);[18]
- 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[19].

[18] Text revised with Protocol Amendment 4 (change no. 8) and Protocol Amendment 5 (see change no. 2).
[19] The last 2 secondary objectives were revised with Protocol Amendment 4 (change no. 17)

5. Study design - amended

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

Following provision of informed consent, patients who fulfill all inclusion criteria and meet none of the exclusion criteria will be treated with ASA 100 mg od[20] 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 bid (see Figure 5–1). 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), and 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[21] after a successful qualifying revascularization procedure and once hemostasis has been assured. All randomized patients 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 first study visit is a screening visit to be performed within 30 days prior to or no more than 10 days after the qualifying revascularization. The second study visit is the randomization visit (randomization will be assigned as T0 on the time axis). The first study drug dose should be administered as close to the time of the randomization visit as possible (See Section 7.4 for additional guidance on dosing at randomization). The screening and randomization visits can be combined into one visit if all tests required for the assessment of all eligibility criteria are available and randomization and dosing can be performed on a single day.[22]

The subsequent on-site study visits at the investigational study site will be completed at 1, 3, 6, and 12 months (Visits 1-4) after T0, and then every 6 months after Visit 4 until the EOT visit.

The study is event-driven, and thus, all patients will be treated (or followed-up in the case of permanent discontinuation of study medication) until the EOT visit. It is estimated that approximately 6,500 patients (3,250 per treatment group) are needed to be enrolled in order to have 1,015 patients experiencing a positively-adjudicated primary efficacy outcome event (for underlying statistical assumptions see Section 10.4). However, this duration may vary depending on the recruitment rate as well as the primary event rate. Due to the event-driven study design, no firm treatment duration can be stipulated for an individual patient. However, the estimated maximum treatment period for an individual patient is approximately 42 months, and the mean treatment duration is expected to be approximately 30 months.

The EOT visit will be performed as soon as possible after announcement of study end or upon individual premature termination of the study. **All efforts must be taken to engage patients to continue to be followed until the end of the trial preferably by regular site visits, or at**

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20 In the following, the background treatment with ASA 100 mg/day will be referred to as "study ASA".

21 Prior to Protocol Amendment 4, “10 days” was “7 days” (change no. 2).

22 Paragraph modified with Protocol Amendment 4 (changes no. 3 and 17).

least by phone contacts, see Section 6.3.1. In all patients, a telephone post-study treatment follow-up visit will be performed one month after the EOT visit.

Patients who have discontinued study drug treatment prematurely will 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 patients until the end of the study via either clinic visits or telephone contacts (see Section 6.3.1).

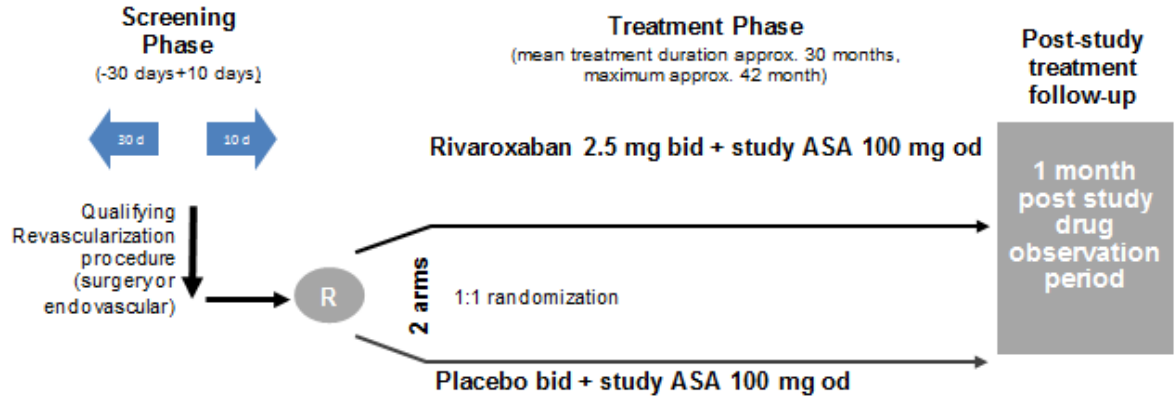
Throughout the study and at all on-site visits, patients will be assessed for the occurrence of study efficacy outcome events and bleeding events. All events including study efficacy outcome, bleeding, and AEs/SAEs meeting the study-specific definitions will be recorded once informed consent (ICF) has been signed and until the post-study treatment follow-up visit. 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 adjudication results will be the basis for the final study analyses. In addition, an Independent Data Monitoring Committee (IDMC) will monitor patient safety during the study and give recommendations to the Executive Committee (EC).

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

For each participating EU country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last patient for all centers in the respective country has occurred. However, as the primary efficacy outcome of this study is event-driven and requires adjudication by an ICAC, the end of the study as a whole will only be reached when the last efficacy outcome event has been adjudicated for patients from all participating clinical sites (EU and non-EU).

The primary completion date for this study according to the FDA Amendment Act is specified in a separate document (not part of this study protocol).

Figure 5–1: Study design - amended[23]



[23] Figure updated with Protocol Amendment 4 (changes nos. 2 and 3)

6. Study population

The study population consists of symptomatic PAD patients of either sex at the age of at least 50 years that have had an endovascular or surgical revascularization. Patients who will be enrolled in this study must meet all of the inclusion criteria and none of the exclusion criteria listed in the following Section 6.1 and Section 6.2, respectively.

6.1 Inclusion criteria - amended

1. Age ≥50 years;
2. [24]Documented moderate to severe symptomatic lower extremity atherosclerotic peripheral artery disease as evidenced by ALL of the following:
   a. clinically, by functional limitations in walking activity, ischemic rest pain, or ischemic ulceration,
   b. anatomically, by imaging evidence of peripheral artery disease distal to the external iliac artery in the index leg within 12 months prior to or at the time of the qualifying revascularization

   AND

   c. hemodynamically in either leg (within 12 months prior to, or at the time of, the qualifying revascularization) by:
      - an ABI ≤ 0.80 or TBI ≤ 0.60 for patients without a prior history of limb revascularization,

        OR

      - an ABI ≤ 0.85 or TBI ≤ 0.65 for patients with a prior history of limb revascularization;
3. Technically successful peripheral revascularization distal to the external iliac artery (surgical and/or endovascular; for definition see Section 9.3.3) for symptomatic PAD within the last 10 days prior to randomization[25];
4. Written informed consent by patient or his/her legal representative;
5. Patient understands and is willing and able to comply with the study instructions and follow-up visit;
6. Negative serum pregnancy test (in women of childbearing potential only);

[24] Inclusion criterion 2 revised with Protocol Amendment 4 (changes no. 4,5 and 20a, b, c)
[25] Inclusion criterion 3 revised with Protocol Amendment 4 (changes no. 2 and 4).

7. [26]Women of reproductive potential must agree to use adequate contraception* when sexually active. This applies for the time period between signing of the informed consent form (ICF) to the last administration of study drug.
   *(*The definition of adequate contraception [with a failure rate of less than 1% per year] will be based on the judgment of the investigator and on local requirements. Acceptable methods of contraception include, but are not limited to: oral contraceptives, contraceptive injections, intrauterine device, double barrier method, male partner sterilization*

6.2 Exclusion criteria - amended

- Exclusion criteria related to PAD:

1. Patients undergoing revascularization for asymptomatic PAD or mild claudication without functional limitation[27] of the index leg
2. Patients undergoing revascularization of the index leg to treat an asymptomatic or minimally symptomatic restenosis of a bypass graft or target lesion restenosis;
3. Prior revascularization on the index leg within 10 days[28] of the qualifying revascularization;
4. Acute limb ischemia (ALI) within 2 weeks prior to the qualifying revascularization.
5. Patients with major tissue loss (defined as significant ulceration/gangrene proximal to the metatarsal heads, i.e. heel or midfoot)[29] in either leg;

- Exclusion criteria related to concomitant and study treatment:

6. Patients requiring treatment with ASA at doses >100 mg;
7. Planned dual antiplatelet therapy (DAPT) use for the qualifying revascularization procedure of clopidogrel in addition to ASA for >6 months after the qualifying revascularization procedure; it is strongly recommended that any course of clopidogrel is kept to the minimum necessary in accordance with local standard of care and international practice guidelines (typically 30 days, or up to 60 days for some drug-coated products or devices), and is only allowed for up to 6 months for complex procedures or devices that in the investigator's opinion require longer use; see section 8.1 for further guidance on clopidogrel; [30]
8. Planned*use of any additional antiplatelet agent other than clopidogrel and ASA after the qualifying revascularization procedure
   (**This exclusion criterion refers to the clinical condition at the time of randomization.*

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[26] Inclusion criterion 7 revised with Protocol Amendment 4 (change no. 21)
[27] Exclusion criterion 1 revised with Protocol Amendment 4 (change no. 15)
[28] Exclusion criterion 3 revised with Protocol Amendment 4 (change no. 7).
[29] Exclusion criterion added with Protocol Amendment 4 (change no. 15)
[30] Exclusion criterion 7 revised with Protocol Amendment 4 (change no. 17) and Protocol Amendment 5 (change no. 3).

The use of DAPT with ASA plus clopidogrel, for new indication(s) occurring after randomization is permitted); [31]

9. Any active clinical condition requiring systemic anticoagulation after the qualifying revascularization;
10. Hypersensitivity or any other contraindication listed in the local labeling for ASA or rivaroxaban;
11. Systemic treatment with strong inhibitors of both Cytochrome P450 isoenzyme 3A4 (CYP3A4) and p-glycoprotein (P-gp) inhibitors (e.g., systemic azole antimycotics, such as ketoconazole [fluconazole is permitted], and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir), or strong inducers of CYP3A4 (e.g., rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine) anticipated after randomization or during the study. [31]

- Exclusion criteria related to bleeding risks or systemic conditions:

12. Medical history or active clinically significant bleeding, lesions, or conditions within the last 6 months prior to randomization, considered to be a significant risk for major bleeding (this may include current medically confirmed gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, current or recent brain or spinal injury, known esophageal varices, vascular aneurysms of the large arteries or major intraspinal or intracerebral vascular abnormalities[32]);
13. Any known hepatic disease associated with coagulopathy or bleeding risk;
14. Any condition requiring dialysis or renal replacement therapy, or a renal impairment at screening assessed with an estimated glomerular filtration rate <15 mL/min/1.73 m^2* (**if a patient's eGFR is <30 mL/min/1.73 m^2 prior to the procedure, it must remain to be >15 mL/min/1.73 m^2 72 hours after the procedure to enroll and randomize the patient*); [31]
15. Confirmed acute coronary syndrome (ACS) within 30 days prior to randomization;
16. Major trauma or accidents within 30 days prior to randomization;
17. Any medically documented history of intracranial hemorrhage, stroke, or transient ischemic attack (TIA);
18. Known active malignancy (as determined through review of medical history), excluding local skin cancer (basal or squamous cell carcinoma);
19. Poorly controlled diabetes (at the discretion of the investigator);
20. Severe uncontrolled hypertension (at the discretion of investigator);
21. Overall life expectancy < 1 year.

- Other exclusion criteria:

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[31] Exclusion criteria modified via Protocol Amendment 5 (change no. 7).

[32] Exclusion criterion 12 revised with Protocol Amendment 4 (change no. 17).

22. Previous assignment to treatment during this study;
23. Previous (within 30 days) or concomitant participation in another clinical study with investigational[33] product (s);
24. Close affiliation with the investigational site; e.g., a close relative of the investigator, dependent person (e.g., employee or student of the investigational site).
25. Breast feeding[34]

6.3 Discontinuation of study medication by subjects and withdrawal criteria

6.3.1 Discontinuation and withdrawal - amended

An excessive rate of patient discontinuations from either treatment or "dropouts" from the study may render the trial uninterpretable. In this trial, ascertainment of study efficacy outcome events, bleeding events, and vital status data are crucial to the primary analysis and must be collected until the end of the study, even if patients are no longer taking study medication. **Therefore, all efforts must be taken to engage patients to comply with all study procedures and to continue to be followed until the end of the trial.** Additionally, study medication compliance will be assessed as defined in Section 7.7.

Patients must be withdrawn from study drug, if any of the following occurs:

- at their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons (even though providing a reason is encouraged), a patient may decline to participate further. The patient will not suffer any disadvantage as a result,
- pregnancy,

Patients may be withdrawn from study drug, if any of the following occurs[35]:

- if, in the investigator's opinion, continuation of the study drug would be harmful to the patient's well-being (e.g. significant decline in cognitive function or renal failure with eGFR<15 mL/min/1.73 m^2),
- at the specific request of the sponsor and in liaison with the investigator (e.g., safety concerns).

Depending on the time point of withdrawal, a withdrawn patient is referred to as either “screening failure” or “dropout” as specified below:

Screening failure: a patient who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before randomization.

Dropout: a patient who discontinues study participation prematurely for any reason, if the patient has already been randomized.

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[33] Exclusion criterion 23 revised with Protocol Amendment 4 (change no. 17)

[34] Exclusion criterion 25 added with Protocol Amendment 4 (change no. 18)

[35] Sentence was added with Protocol Amendment 4 (change no. 16).

Reasons for discontinuing study medication should be solicited and documented. **Study medication or study ASA will not be routinely discontinued in patients reaching a potential primary efficacy event unless there is a safety concern or a clear indication for an alternative antithrombotic therapy, as determined by the local investigator.**

If study medication and/or study ASA will be temporarily interrupted or permanently discontinued, the investigator will document the reason on the electronic case report form (eCRF), and if applicable in the patient's medical records/source documents. The study medication and/or study ASA will be restarted as soon as medically justified (in the opinion of the investigator). There is no defined maximum limit for temporary treatment interruption, however, the date of temporary treatment discontinuation, date of re-starting treatment and the reason for temporary discontinuation will be documented in the eCRF.

All patients who permanently discontinue study medication and/or study ASA and have not withdrawn consent will remain in the study, and are expected to complete all on-site study visits as originally scheduled. If a patient permanently discontinues study medication and is unwilling or unable to attend regular study visits at the study site, the investigator and patient must determine which of the follow-up options the patient is able and willing to comply with. The patient will be approached to provide consent for further follow-up at the time of withdrawal. Options for follow-up of these patients are listed below, in descending order of preference:

1. Patient will be contacted by phone at the regular study visit intervals.
2. Patient allows his/her general practitioner (with a signed release of medical information) or a family relative to be contacted (if allowed in respective country) at the regular study visit intervals.
3. Patient will be contacted once at the end of the study.
4. No further contact.

For patients who withdraw consent for any kind of follow-up, the patient's vital status will be obtained at study end through applicable information sources according to local guidelines and as allowed by local regulations. In all cases, the reason for withdrawal must be recorded in the eCRF and in the patient's medical records.

If a patient fails to return for a study visit or is suspected to be lost to follow-up, the investigator should explore all possible options to contact the patient. The investigator should ask the patient at the time of enrollment for the contact details of an alternate contact (e.g., relative or friend) in case the patient cannot be reached. The site must document all attempts to try to contact the patient and alternate contact in the medical records/source documents. If all attempts fail (depending on local legislation), publically available information such as death registries or other registries may be accessed or private investigation to locate a patient may be initiated.

Any patient removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

6.3.2 Replacement

No patient replacements are permitted in this study.

6.4 Subject identification

Each patient will be allocated a unique patient identification number after informed consent is obtained, and an additional randomization number will be assigned by IxRS at the time of randomization. This randomization number will allow subsequent identification of treatment allocation.

The patient number is a 9 digit number consisting of:

Digits 1 to 2 = Country code

Digits 3 to 5 = Center number within the country

(Digits 1 to 5 = Trial unit)

Digits 6 to 9 = Current patient number within the center

7. Treatments

7.1 Treatments to be administered - amended

Study treatment assignment will be double-blind. Study treatment consists of study medication (rivaroxaban or matching placebo) in addition to study ASA, which is also dispensed by the study. Eligible study patients will be randomized in a ratio of 1:1 to one of the 2 following treatment arms:

Rivaroxaban group:

Rivaroxaban 2.5 mg bid (5 mg/day, immediate-release film-coated tablets for oral administration)
+
ASA 100 mg od (enteric coated tablets for oral administration)

Reference group:

Rivaroxaban-matching placebo bid (tablets for oral administration)
+
ASA 100 mg od (enteric coated tablets for oral administration)

In either treatment group, post-procedural concomitant treatment with clopidogrel will be allowed as described in section 8.1.[36]

The estimated mean treatment duration will be 30 months (maximum treatment duration 42 months) in either treatment arm.

7.2 Identity of study treatment

Study medication and study ASA will be labeled according to the requirements of local law and legislation. Label text will be approved according to the Sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

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[36] Text revised with Protocol Amendment 4 (change no. 17)

For all study medication and study ASA, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study medication and study ASA can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the Sponsor's Quality Assurance group.

A complete record of batch numbers and expiry dates of all study medication and study ASA as well as the labels will be maintained in the Sponsor's study file.

7.3 Treatment assignment - amended

Allocation to treatment arms will be done centrally by IxRS. Allocation will be performed in a ratio of 1:1 to each study treatment arm and will be stratified in one of 3 strata by:

- surgical revascularization,
- endovascular revascularization with clopidogrel,
- endovascular revascularization without clopidogrel.

Given potential differences in natural history resulting from procedure type, variation in medical practice, and concomitant therapy that may affect treatment outcome.

The clopidogrel use defining the randomization strata refers to actual clopidogrel use, at randomization, as adjunct treatment for the qualifying revascularization. [37] Specific procedures for treatment assignment through the IxRS will be described in the IxRS manual.

7.4 Dosage and administration - amended

Patients will be provided with high-density polyethylene (HDPE) bottles containing immediate-release film-coated tablets of study medication rivaroxaban 2.5 mg (or matching placebo) and HDPE bottles containing enteric-coated tablets of study ASA 100 mg. The dose amount distributed per on-site visit will be sufficient to cover a period of between the study visits at the investigational site.

All study medication treatments will be taken orally. Study medication (rivaroxaban or placebo) will be taken twice daily (generally in the morning and in the evening, approximately 12 hours apart) and study ASA will be taken once daily, generally in the morning.

If a dose of study medication is missed and less than 6 hours have elapsed since the time that the missed dose was due, it should be taken immediately. If more than 6 hours have elapsed since the missed dose was due, the dose should be skipped and the next dose of study rivaroxaban or placebo should be taken according to schedule. A missed dose from a previous calendar day should not be taken with the current dose.

For patients using a parenteral anticoagulant, the timing of the first dose of study medication administration should be no sooner than: 2 hours after final dose bivalirudin, 4 hours after final dose of intravenous unfractionated heparin, eptifibatide, or tirofiban, 12 hours after final

[37] Text modified via Protocol Amendment 5 (change no. 7)

dose of other intravenous or subcutaneous anticoagulants (e.g., enoxaparin, dalteparin) and 24 hours after final dose of abciximab or fondaparinux. Depending on the patient and the clinical setting, initiation of study medication in a patient with low risk of bleeding, who is on low dose subcutaneous anticoagulants sooner than 12 hours may be appropriate and permissible (consult Study Helpline).

Clopidogrel (at a dose that is consistent with the site/country's standard of care) may be used at the discretion of the investigator, as described in Section 8.1.[38]

7.4.1 Dose modifications

The investigator should interrupt study medication and/or study ASA for a given patient if continuation is deemed to be detrimental to the patient's well-being. All patients who interrupt study medication and/or study ASA should resume treatment when possible. If there is concern that the patient may be intolerant of study treatments or if the patient is reluctant to take the full dose of study medication, a possible approach to restarting study medications is to reduce the frequency of dosing to once-daily or alternate-daily.

Irrespective of whether or not treatment is resumed, all patients must be followed according to the study protocol until the end of the study. Permanent study drug discontinuation should be recorded on the eCRF, giving the date and primary reason for stopping the study medication and/or study ASA. If one of the study treatments needs to be interrupted, other study treatments should be continued. For example, if study medication is interrupted, study ASA should be continued.

This section provides a general guide for investigators on the management of patients who develop intercurrent illnesses or bleeding during the course of the study. The guidance provided in this section does not replace clinical judgment nor usual care in determining the appropriate management strategy for individual patients.

The following sections provide general guidance for use of rivaroxaban. For use of ASA, please refer to applicable guidelines and local production information.

7.4.2 Guidance for the treatment of subjects who require an invasive procedure

If a patient requires an invasive procedure that is associated with a standard or high risk of bleeding (i.e., any procedure that is not considered "minor"), study medication must be interrupted.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, study medication should be stopped **at least 12 hours** before the intervention, if possible and based on the clinical judgment of the physician. If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention. Study medication should be restarted after the invasive procedure or surgical intervention as soon as possible, provided the clinical situation allows and adequate hemostasis has been established.

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[38] Text revised with Protocol Amendment 4 (change no. 17)

7.4.3 Guidance for the treatment of subjects who require coronary artery bypass graft (CABG) surgery – amended

Patients who are scheduled for CABG surgery during the course of the trial, ideally should interrupt study medication at least 12 hours before coronary artery bypass graft surgery in order to minimize the risk of bleeding.

Study medication may be interrupted and/or non-study ASA may be used at the discretion of the investigator. The timing of resumption of study medication after surgery is at the discretion of the investigator but, in general, study medication or study ASA should be resumed once the chest tubes are removed and hemostasis is assured. Study medication should be interrupted if patients require systemic anticoagulation.[39] In all cases, the goal should be to resume study medication as soon as it is clinically warranted prior to being discharged from the hospital.

7.4.4 Guidance for the treatment of subjects who develop an acute coronary syndrome and those who require percutaneous coronary intervention with stenting - amended

[40] Study medication should be temporarily interrupted in patients who require anticoagulant or DAPT because of an ACS event or for percutaneous coronary intervention (PCI) with stenting. Peri-procedurally, standard antiplatelet therapy, including ASA and clopidogrel (or other P2Y12 antagonists such as prasugrel or ticagrelor) can be administered according to usual practice. Study ASA may be continued. Standard anticoagulant therapy can be initiated without regard to the timing of the most recent dose of study medication because the dose of rivaroxaban being tested in this trial is significantly lower than the 15 or 20 mg dose administered for stroke prevention in non-valvular atrial fibrillation and the half-life of rivaroxaban is short, only 5-13 hours.

Following the procedure, the decision and timing to resume study medication are at the discretion of the treating physician and the investigator. If medically indicated, study medication may be used along with DAPT with clopidogrel as described in section 8.1, or interrupted until patient no longer requires DAPT.

7.4.5 Guidance for the treatment of subjects who overdose on study medication

A specific antidote for rivaroxaban is not available. If rivaroxaban overdose is suspected, the use of activated charcoal up to 8 hours after overdose to reduce absorption may be considered. Due to its low solubility, rivaroxaban absorption plateaus at doses of 50 mg and above, thus limiting exposure in the majority of patients.

7.4.6 Guidance for the treatment of subjects who experience a major bleed

The management of bleeding in patients receiving study medication is supportive, as rivaroxaban does not have a specific antidote. Temporary discontinuation of rivaroxaban is

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[39] Text revised with Protocol Amendment 4 (change no. 17)

[40] Text revised with Protocol Amendment 4 (change no. 17)

expected to be sufficient to control bleeding in most cases because the drug half-life is only 5-13 hours. Local measures should be applied if needed to control bleeding (e.g., local pressure, endoscopy and injection of a bleeding vessel, as in embolization) and intravenous fluids and blood transfusion support should be provided as indicated. In the rare case of life-threatening bleeding, the investigator may consider obtaining advice from a hematologist. Animal studies suggest that both prothrombin complex concentrates, activated prothrombin complex concentrate (APCC), or recombinant factor VIIa partially restore hemostasis following treatment with factor Xa inhibitors such as rivaroxaban, and a randomized trial involving healthy patients treated with rivaroxaban has demonstrated that prothrombin complex concentrates reverse prolongation of the prothrombin time. Rivaroxaban cannot be dialyzed as it is highly protein bound.

7.4.7 Guidance for the treatment of subjects who have impaired renal function

Patients with impaired renal function (i.e. <60 mL/min/1.73 m^2 but ≥15 mL/min/1.73 m^2 are eligible for the study (see Section 6.2). If a patient's eGFR is <30 mL/min/1.73 m^2 prior to the index procedure, to enroll and randomize the patient the eGFR must be confirmed to ensure that the eGFR remains >15 mL/min/1.73 m^2, at least 72 hours after the procedure.
During the study, in subjects with baseline eGFR <30 mL/min/1.73 m^2, renal function should be monitored as per standard of care, tailored to the need of the subject. Study medication should be interrupted or permanently discontinued if the eGFR should fall below 15 mL/min/1.73 m^2.

7.5 Blinding

Study medication (rivaroxaban or matching placebo) assignment will be double-blind. Study treatment consists of study medication (rivaroxaban or matching placebo) in addition to study ASA. Additional details of emergency unblinding procedure can be found in the IxRS operation manual.

Unblinding should only be undertaken by the investigator when it is deemed medically necessary for the patient's safety and will be done via the IxRS system. If there is an uncertainty with respect to an unblinding decision, the investigator may contact the 24-hour Study Helpline (independent of the sponsor).

However, the Study Helpline contact should not delay emergency treatment of the patient. Examples that should trigger a Helpline discussion include life-threatening bleeding or bleeding requiring surgical intervention.

In compliance with applicable regulations, in the event of a SUSAR (see Section 9.6.1.4) related to the blinded treatment, the patient's treatment code will usually be unblinded before reporting to the health authorities, ethic committees, and investigators.

7.6 Drug logistics and accountability

All study medication and study ASA need to be stored at the investigational site according to the labeled storage advice and in accordance with Good Clinical Practice (GCP) and GMP requirements. Study medication and study ASA should not be stored above 30°C. The study medication and study ASA are to be kept in a limited access and secure area that cannot be

accessed by unauthorized personnel. Site personnel will confirm receipt of study medication and study ASA via IxRS and will use study medication and study ASA only for this study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of the study medication and study ASA must be properly documented according to local regulation and specified procedures.

Written instructions on medication destruction for unused study medication and study ASA returned to the sites by the patient as well as undispensed study medication and study ASA will be made available to affected parties as applicable.

7.7 Treatment compliance

Treatment compliance for the study medication and study ASA will be assessed at each study visits by interview and by counting the tablets returned by the patient to the site and will be documented in the eCRF. Any discrepancies between actual and expected amount of returned study medication and study ASA must be discussed with the patient at the time of the visit, and any explanation must be documented in the eCRF and, if appropriate, in the patient's medical record.

The date of first dose, the last dose, and dose interruptions of either study medication or study ASA will be reported in the eCRF. Patients with temporary interruption of study medication and/or ASA for medical reasons should restart study medication and/or study ASA administration again as soon as medically indicated.

8. Non-study therapy

8.1 Prior and concomitant therapy - amended

Generally, all prior (within 30 days prior to randomization[41]) and concomitantly taken drugs (as specified in the eCRF) need to be recorded in the eCRF. During the study, concomitant therapy will be recorded at the study visits, or at the time of occurrence of any efficacy outcome events, bleeding events, and SAEs. In addition, any remedial therapy for non-serious-AEs (if AEs are subject to reporting) should be documented.

Clopidogrel and other non-study antiplatelet treatment[42]

Patients who enter the study receiving additional antiplatelet therapy will have non-study antiplatelet therapy discontinued when study medication is started.

If deemed required by the investigator, the use of clopidogrel concomitantly with study drugs is allowed at the time of randomization. It is strongly recommended that any course of clopidogrel is kept to the minimum necessary to comply with local standard of care and international practice guidelines (typically 30 days, or up to 60 days for some drug-coated products or devices). Clopidogrel will not be supplied as a study medication.

During the course of the study, for enrolled patients who require use of clopidogrel for a new indication (e.g., indication for PCI with or without stenting), use of clopidogrel is allowed

41 Text revised with Protocol Amendment 4 (change no. 17)

42 Text in this section was revised with Protocol Amendment 4 (change no. 9) and Protocol Amendment 5 (change no. 3).

(see Section 7.4.4). At the discretion of the investigator, study medication may be used along with clopidogrel or interrupted until the patient no longer requires clopidogrel. The duration of clopidogrel use should follow standard of care and applicable international guidelines.

Treatment with other P2Y12 antagonists, such as prasugrel or ticagrelor may be administered according to usual practice, but the study drug must be interrupted if such drugs are used long-term.

The concomitant use of non-steroid anti-inflammatory drugs (NSAIDs) and non-study antiplatelet therapy during the study (except clopidogrel in the initial study phase) is strongly discouraged since it increases the risk for bleeding. However, if an NSAID drug is indicated, the lowest possible dosage must be selected.

For patients at risk for ulcerative gastrointestinal disease or bleeding or who develop symptoms of these complications during the study, an appropriate gastro-protective prophylactic treatment may be recommended by the investigator, but will not be supplied as study medication.

Systemic anticoagulation

The following drugs are regarded as relevant in terms of influencing coagulation:

- unfractionated heparin and its derivatives (i.e., including low molecular weight heparin (LMWH)),
- vitamin K antagonists,
- novel or Non-VKA oral anticoagulants (NOACs),
- fibrinolytic treatment is allowed during the intervention/surgery, but it must be stopped no later than 24 hours before randomization into the trial.

The use of any of these drugs needs to be recorded in the eCRF.

Patients with a foreseeable need for systemic anticoagulation after the qualifying revascularization procedure should not be enrolled in the study (see Section 6.2). Patients who develop a need for anticoagulant therapy during the study period (e.g., thromboprophylaxis in patients undergoing major orthopedic surgery, acute VTE, atrial fibrillation, mechanical aortic valve replacement, etc.) must interrupt study treatment with rivaroxaban or placebo, while study ASA might be continued at the discretion of the investigator. Study treatment should be restarted in patients who no longer have a need for non-study anticoagulant therapy as soon as possible after the discontinuation of the non-study anticoagulant therapy (e.g., after completion of anticoagulant thromboprophylaxis or anticoagulant treatment for VTE). Bridging or temporary overlap of study medication with anticoagulant therapy may be appropriate, considering the patient's need, risk, and clinical setting. In case of questions, please consult the Study Helpline.

Prohibited therapy while on study medication

- systemic treatment with strong inhibitors of both CYP3A4 and P-gp inhibitors (e.g., systemic azole antimycotics[43], such as ketoconazole, and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir), or strong inducers of CYP3A4 (e.g., rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine) at the time of screening or their anticipated use during the study;
- use of antiplatelet therapy other than the protocol specified background antiplatelet therapy of study ASA or clopidogrel is prohibited during the study. This includes drugs with known significant antiplatelet effects such as cilostazol, prasugrel and ticagrelor. [44]
- additional anticoagulant(s) (e.g., warfarin sodium or vitamin K antagonists, heparins, Factor II or Xa inhibitors) concomitantly with study medication are prohibited.[45]
- NSAID (except ASA) may be used concomitantly on a temporary basis, but should be avoided for chronic use (> 4 weeks) during the study;
- any non-study ASA use will not be permitted. For management of CABG and PCI during the study, refer to Section 7.4.3 and Section 7.4.4. Other non-ASA medications should be used for conditions such as pain relief and fever reduction.

These prohibited therapies may be administered on a temporary basis in combination with the study drug if deemed medically appropriate. In general,[46] the investigator should consider temporarily discontinuing study medication if the treatment could result in an increased risk of bleeding (e.g., strong inhibitors of both CYP3A4 and P-gp, or anticoagulants). Study drug medication may be restarted after the prohibited therapy has been discontinued and after completion of a suitable washout period at the investigator's discretion.

Study medication should be temporarily interrupted, if the patient:

- undergoes PCI, CABG, or any other surgical procedure, or medical condition that may require temporary interruption of study drug, or use of prohibited therapy due to bleeding risk or use of open-label anticoagulants,
- experiences a significant bleeding event,
- develops a new neurological deficit or significant alteration in mental status,
- develops a platelet count <50,000/μL,
- has any serious adverse event possibly related to or exacerbated by study drug administration,
- requires a prohibited therapy on a temporary basis.

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43 Systemic treatment with fluconazole is permitted.
44 Bullet point revised with Protocol Amendment 4 (change no. 22a).
45 Bullet point revised with Protocol Amendment 4 (change no. 22b and 22c).
46 Text revised with Protocol Amendment 4 (change no. 17).

Study medication can be resumed at a time when in the opinion of the investigator it is safe to do so.

Discontinuation of Study Drug for a Vascular Procedure

Table 8–1 depicts the approximate equivalent dose of subcutaneous enoxaparin (mg/kg) relative to rivaroxaban 2.5 mg at given time points following its administration, and should be used to assist the investigator in deciding which dose of enoxaparin or equivalent dose of another antithrombotic agent to administer in the event when a patient may have to undergo an emergency interventional coronary procedure or pharmacologic reperfusion while receiving study drug.

Table 8–1: Comparative antithrombotic effect at given time points following rivaroxaban 2.5 mg administration to subcutaneous enoxaparin doses

Time after 2.5 mg Rivaroxaban Administration	Equivalent Enoxaparin Dose
3 h	0.15 mg/kg
6 h	0.1 mg/kg
> 9 h	0 mg/kg

Source: [Mega et al. 2012] [47]

When thrombolysis is required within 3 hours of the last study drug administration, it may be necessary to unblind the patient at the discretion of the investigator to estimate the dose of enoxaparin to be administered; in the case the patient is in the rivaroxaban treatment group, the subcutaneous dose of enoxaparin should be adopted as given in Table 8–1.

In case of urgent PCI for acute ischemic event, the investigator should discontinue study medication and initiate therapy with non-study ASA prior to PCI with non-enteric coated formulation. The loading dose of non-study ASA may be considered. In addition, consider intravenous administration of 0.5 mg/kg of enoxaparin or its antithrombotic equivalent in patients who undergo PCI. In the event that a patient requires a non-emergency revascularization procedure (PCI or CABG), study medication should be stopped approximately 24 hours before the procedure, if possible, and appropriate anticoagulant or antiplatelet therapy should be instituted as medically indicated (including DAPT).

[48]Depending on the bleeding risk, the patient may, at the discretion of the managing physician, resume study medication thereafter, but no earlier than approximately 12 hours after the arterial sheath has been removed (for patients undergoing PCI) or after the post-procedural drains have been removed (for patients undergoing CABG surgery), and the last dose of parenteral anticoagulant therapy has been administered.

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[47] Table derived from Attachment 6 of the study protocol of the ATLAS ACS 2 TIMI 51 trial (The second trial of Anti-Xa Therapy to Lower cardiovascular events in Addition to standard therapy in Subjects with Acute Coronary Syndrome), which is online accessible through the website of the New England Journal of Medicine in the supplementary material section (last accessed on 14-FEB-2015): <http://www.nejm.org/doi/suppl/10.1056/NEJMoa1112277/suppl_file/nejmoa1112277_protocol.pdf>

[48] First sentence was removed with Protocol Amendment 4 (change no. 22d).

8.2 Post-study therapy

After discontinuation of study medication (either at study end or in case of permanent premature discontinuation), initiation of standard of care therapy is the responsibility and at the discretion of the investigator.

8.3 Background non-antithrombotic therapy

Given the prevalence of potentially modifiable risk factors and concomitant conditions such as diabetes, hyperlipidemia, hypertension, or smoking in this study population, aggressive treatment and life-style modification are clinically warranted. It is recommended that patients be treated in accordance to standard of care and applicable international/local guidelines.

9. Procedures and variables

9.1 Tabular schedule of evaluations - amended

Please note: As this is an event-driven study, patients participating in this study will have different numbers of study visits.

Patients will be assessed for study participation prior to, or after, the qualifying revascularization whereas this procedure is not considered to be a study visit. [49]On-site study visits for the patients at the investigational site are planned at Screening, Randomization, 1, 3, 6, and 12 months after randomization, and then every 6 months until the end of the study. Upon announcement of study end, patients will come to the clinic for a final on-site EOT visit followed by a telephone contact (post-study treatment follow-up visit) one month later.

The following visit abbreviations are used in the description of the visit schedule:

ScV: Screening visit (to be performed up to 30 days prior to but no later than 10 days after Rev; screening procedures can be performed over multiple days if necessary)[50]

Rev: Day of the qualifying revascularization procedure (not considered a study visit).

RxV: Randomization visit (time point of randomization = [T0]), to be performed as soon as possible but no later than 10 days[51] after Rev once hemostasis is assured.

V1: Visit 1, to be performed 1 month after RxV with an accepted time window of ± 10 days.

V2-4: Visits 2, 3, and 4; to be performed 3, 6, and 12 months after RxV with an accepted time window of ± 4 weeks.

V5-Vx: Visit 5 to Visit 5+n (where n is the number of additional treatment phase on-site visits beyond Visit 5) to be performed at regular intervals of 6 months with an accepted time window of ± 4 weeks; continued until individual premature

[49] Sentence revised with Protocol Amendment 4 (change no. 17).
[50] Revised with Protocol Amendment 4 (change no. 3).
[51] Prior to Protocol Amendment 4, 10 days was 7 days (change no. 2).

permanent termination of the study (not study drug treatment; see Section 6.3) or announcement of study end.

EOT: End of treatment visit, to be performed within 4 weeks after announcement of study end or upon individual termination of the study (not premature study drug discontinuation; see Section 6.3). No further study medication will be dispensed at this visit.

PS-FU: Post-study treatment follow-up visit by phone call, to be performed one month after the EOT visit with an accepted time window of ± 1 week.

[52]Clinic visits or procedures should be scheduled as close to the specified interval as possible, and preferably within the defined window. If it is not possible for the patient to return within the visit "window", or perform the required study procedures especially due to unforeseen circumstance or technical feasibility beyond the control of the patient or the study center, then the visit or procedure should be scheduled as close to the interval as is convenient for the patient and the study center.

52 Paragraph revised with Protocol Amendment 4 (change no. 17).

Table 9–1: Schedule of assessments - amended

Timelines	ScV [a]	Qualifying revascular-ization (Rev)	RxV [a] (T0)	Treatment Phase V1 1 Mo	V2 3 Mo	V3 6 Mo	V4 12 Mo	V5-Vx every 6 Mo	EOT visit [b]	PS-FU 1 Mo post EOT
Visit Window (weeks if not otherwise specified)	**-30 days before, to +10 days after, Rev[53]**		**Up to +10 days after Rev[54]**	**±10 days**	**±4**	**±4**	**±4**	**±4**		**±1**
Type of Visit	**Visit**		**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	☎
Informed consent	●									
Demographics	●									
Medical / surgical history	●									
Laboratory tests [c]	●									
Serum pregnancy test [d]	●									
Inclusion/Exclusion	●									
Revascularization procedure (surgical or endovascular)		♦								
Documentation of revascularization details			●[55]							
Randomization (IxRS)			●							
Concomitant medications [e]	●		●	●	●	●	●	●	●	
1st study drug			●							
Drug dispense			●	●	●	●	●	●		
Drug accountability				●	●	●	●	●	●	
Vital Signs	●		●	●	●	●	●	●	●	
Study efficacy outcomes	● ←			continuous reporting						→
Study safety outcomes (bleeding events)	● ←			continuous reporting						→
AE/SAE reporting [f]	●		●	●	●	●	●	●	●	●
ABI/TBI[h]	● [g]			●	●	●	●	●	●	
(footnotes are provided on the next page)										
Questionnaires (EQ-5D,			●	●	●	●	●	●	●	

53 Schedule revised with Protocol Amendment 4 (change no. 2).
54 Schedule revised with Protocol Amendment 4 (change no. 3).
55 Schedule revised with Protocol Amendment 4 (change no. 17).

Table 9–1: Schedule of assessments - amended

Timelines	ScV [a]	Qualifying revascular -ization (Rev)	RxV [a] (T0)	Treatment Phase V1 1 Mo	V2 3 Mo	V3 6 Mo	V4 12 Mo	V5-Vx every 6 Mo	EOT visit [b]	PS-FU 1 Mo post EOT
Visit Window (weeks if not otherwise specified)	**-30 days before, to +10 days after, Rev[53]**		**Up to +10 days after Rev[54]**	**±10 days**	**±4**	**±4**	**±4**	**±4**		**±1**
WIQ, HCRU) PAD symptom status[56]										
Vital status										●

[57] ♦ = non-study procedure (*change no. 17*); ● = study procedure to be performed at specified visits; ☎ = post-study treatment telephone contact

Abbreviations: ABI/TBI = Ankle (Toe) - Brachial - Index; AE = adverse event; EOT = end of treatment; EQ-5D = European Quality of Life-5 Dimensions questionnaire; IxRS = Interactive Voice and Web Response System; Mo = month; V = visit; Rx = randomization; SAE = serious adverse event; Sc = Screening; WIQ = Walking Impairment Questionnaire, HCRU= HealthCare Research Utilization (see Section 9.7.3) (change no.17)

a: Screening visit can be performed at the same time as randomization visit, if all required tests for eligibility criteria are available at that time. Screening period is 30 days before or up to 10 days (*change no. 3)* after the revascularization procedure. Randomization should be done as soon as possible (but within 10 days [*change no. 2*]) after the qualifying revascularization procedure.

b: End of treatment visit is to be performed within 4 weeks after announcement of study end, or once the patient has permanently withdrawn from the study.

c: Laboratory tests required to verify the eligibility criteria (creatinine/eGFR) are to be collected per the site's standard of care and assessed through a local lab. Creatinine/eGFR must not be older than 30 days prior to the qualifying revascularization (*change no. 10*). If the patient's eGFR is <30 mL/min/1.73 m^2 prior to the procedure, it must remain to be >15 mL/min/1.73 m^2 72 hours after the procedure in order (*change no. 17*) to enroll and randomize the patient.

d: Required in women of childbearing potential only. A pregnancy test must not be older than 7 days prior to randomization.

e: Planned post-procedural concomitant clopidogrel allowed at the discretion of the investigator, see Section 8.1

f: Only AE/ SAEs not exempted from adverse event reporting and specified in the protocol need to be documented (see Section 9.6.1.3 (change no.17).[58]

g: ABI/TBI values used at screening may be historical (captured in the patient's medical history), but must not be older than 12 months prior to the qualifying revascularization procedure (*change no. 5*). If an ABI/TBI is performed during screening to assess eligibility, it must be completed prior to, or at the time of, the qualifying revascularization (*change no. 6*).[59]

h: ABI/TBI assessments performed after informed consent is obtained must be performed per the guidance in the ABI/TBI Site Manual.[60]

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56 Schedule revised with Protocol Amendment 4 (change no. 12).

57 Single footnotes of Table 9-1 were revised with Protocol Amendment 4. All changes are included behind the respective text for better readability.

58 Footnote revised with Protocol Amendment 5 (change no. 7).

59 Footnote revised with Protocol Amendment 5 (change no. 7).

60 Footnote added with Protocol Amendment 5 (change no 5).

9.2 Visit description

9.2.1 Timing of assessments

9.2.1.1 Screening Visit (ScV): 30 days before, or up to 10 days after qualifying revascularization procedure - amended

[61]The ScV is required to assess the eligibility of the patient. After obtaining signed informed consent, the investigator will review or perform all medical evaluations required to verify the patient's eligibility for study participation as defined in the inclusion and exclusion criteria. Adverse events reporting begins once the informed consent has been signed.

Demographic data and medical history (including PAD risk factors and vascular disease history) will be recorded at Screening. Laboratory tests should be performed according to the site specific standards, but must, at minimum, include creatinine and eGFR, and a serum pregnancy test in women of childbearing potential. Results of laboratory measurements (ideally obtained during the hospital admission for the qualifying revascularization) should not be older than 30 days prior to the qualifying revascularization; otherwise, tests would need to be repeated. If the site's local laboratory report does not provide eGFR, this value should be calculated (e.g. using the Modification of Diet in Renal Disease [MDRD] formula). All laboratory tests will be performed locally as no central laboratory is involved in this study.

The following measures/documentations will be performed at the screening visit:

- obtaining informed consent;
- documentation of demographic characteristics (for details see Section 9.3.1);
- documentation of medical history (for details see Section 9.3.2) and surgical history;
- review laboratory test data for the patient, if creatinine/eGFR assessments were performed more than 30 days prior to the qualifying revascularization, they must be redrawn and if serum pregnancy test (females with childbearing potential only)[62]was performed more than 7 days ago prior to the qualifying revascularization a repeat pregnancy test must be performed;
- evaluate for all inclusion- and exclusion criteria;
- documentation of prior (within the last 30 days prior to randomization[63]) and concomitant medication. Chronic treatment with prescription antiplatelet therapies (except already ongoing treatment with low-dose ASA that can be continued as study ASA 100 mg od) should be stopped at the time of randomization;
- assess vital signs (blood pressure, pulse rate);
- check for the occurrence of AEs/SAEs since the signing of the ICF (only AEs/SAEs not exempted from AE/SAE reporting need to be reported; for details see Section 9.6.1.3);

61 First two paragraphs revised with Protocol Amendment 4 (changes no. 3 and 10).
62 Sentence revised with Protocol Amendment 4 (change no. 17).
63 Sentence revised with Protocol Amendment 4 (changes no. 10 and 17).

- perform ABI (or TBI) if no ABI/TBI data are available for the patient within the last 12 months[64] prior to the qualifying revascularization; ABI/TBI assessments performed after informed consent is obtained must be performed per the guidance in the ABI/TBI Site Manual.[65]

If the patient is eligible for study participation, the site investigator should make all organizational arrangements required for prompt randomization of the patient to study treatment as soon as feasible, but no more than 10[66]days after the qualifying revascularization procedure (for treatments to be administered, see Section 7.1).

9.2.1.2 Randomization visit (RxV): 0-10 days after the qualifying revascularization procedure - amended

[67]After meeting all inclusion criteria and none of the exclusion criteria, eligible patients will be randomized by accessing the IxRS system and receive study medication and study ASA as soon as feasible, but no more than 10 days after the qualifying revascularization procedure. The first dose of study medication should be given immediately, but no more than 24 hours after randomization, if study drug can be safely administered (see Section 7.4). Planned additional treatment with clopidogrel after the qualifying revascularization procedure is allowed at the discretion of the investigator, as described in section 8.1.[68]

The following measures/documentations will be performed at the randomization visit:

- randomization of patient (must be performed prior to all other randomization study visit procedures);[69]
- documentation of the details about the qualifying revascularization and its success;[70]
- If laboratory evaluations have been performed and are available per standard or usual care of the subjects in the recent past that reflect baseline hematologic, glucose metabolic, liver, and renal functions, record the relevant and available indices in the eCRF (HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, ALT(SGPT), AST(SGOT), total bilirubin, hemoglobin, hematocrit, platelet count). The serum creatinine value used to assess eligibility and corresponding eGFR should also be entered;[71]
- dispensing of study medication and study ASA with patient instruction;
- administration of first study medication treatment dose (on-site);
- documentation of any changes in concomitant medication since the last study visit;
- assess vital signs (blood pressure, pulse rate);

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64 Timepoint for ABI (TBI) changed with Protocol Amendment 4 (changes no. 5 and 10).
65 This bullet point was modified with Protocol Amendment 5 (change no. 5).
66 Sentence revised with Protocol Amendment 4 (change no. 3).
67 Section revised with Protocol Amendment 4 (changes no. 2 and 17)
68 Last two sentences revised with Protocol Amendment 4 (change no. 17).
69 Sentence revised with Protocol Amendment 4 (change no. 17).
70 Sentence revised with Protocol Amendment 4 (change no. 17).
71 Bullet added with protocol Amendment 4 (change no. 19)

- check for the occurrence of study efficacy outcome events since the last study visit (these pre-randomization events should be documented on the outcome pages and forwarded by expedited means to the Sponsor's PV; see Section 9.6.1.3);
- check for the occurrence of study safety outcome events (bleeding events) since the last study visit (these pre-randomization events should be documented on the outcome pages and forwarded by expedited means to the Sponsor's PV; see Section 9.6.1.3);
- check for the occurrence of AEs/SAEs since the last study visit; for events exempted from AE/SAE reporting, see Section 9.6.1.3);
- assess the patient's PAD Symptom Status.
(This assessment, as well as the QoL assessment and Walking Impairment Questionnaire, should reflect the time period prior to the qualifying revascularization procedure);[72]
- QoL assessment with EQ-5D;
- Walking Impairment Questionnaire;
- remind patient to return with the study medication and study ASA dispensed bottles at their next visit.

Note: Screening and randomization visits can be combined into one single visit, provided that all required information for the patient eligibility assessment are available at that time (e.g., eGFR values). Study endpoint evaluations and safety evaluations will start from time of signing the ICF. The patient will be instructed to report any hospitalization or other significant illness to the investigator on an ongoing basis during the entire course of the study in order to allow a timely reporting of study efficacy outcome events, bleeding events, and other AEs/SAEs.

9.2.1.3 Treatment phase: Regular study visits from Visit 1 onwards - amended

Patients will return to the study site for the first on-treatment visit one month following randomization (Visit 1, with a permitted time window of ± 10 days). Further regular treatment visits (all with a permitted time window of ± 4weeks) will be performed 3 months (Visit 2), 6 months (Visit 3), and 12 months (Visit 4) after randomization, and then every 6 months until the study end will be announced (see Table 9–1).

At each on-site visit in the treatment phase, patients will be asked about the occurrence of potential study efficacy outcome events, bleeding events, and AEs/SAEs. If a suspected study efficacy outcome event or bleeding event is reported, the respective eCRF page will be completed and an adjudication package expeditiously compiled and submitted to the ICAC.

The following measures/documentations will be performed at each study visit:

- check for the occurrence of study efficacy outcome events since the last study visit;
- check for the occurrence of bleeding events since the last study visit;

[72] Last sentence added with Protocol Amendment 4 (change no. 12).

- complete all eCRF outcome event, bleeding event and Health Care Resource Utilization (HCRU see Section 9.7.3) pages if applicable[73]
- check for the occurrence of AEs/SAEs since the last study visit (for events exempted from AE/SAE reporting, see Section 9.6.1.3);
- document any changes in concomitant medications since the last study visit;
- assess the patient's PAD Symptom Status;[74]
- If the following laboratory evaluations have been performed since the last study visit and are available in the medical record, it is requested that this information be recorded in the eCRF: HbA1c, creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, ALT(SGPT), AST(SGOT), total bilirubin, hemoglobin, hematocrit, platelet count;[75]
- QoL assessment with EQ-5D (questionnaires should be completed before the other visit procedures);
- Walking Impairment Questionnaire (questionnaires should be completed before the other visit procedures);
- assess vital signs (blood pressure, pulse rate);
- perform ABI (or TBI);[76]
- collect study medication and study ASA bottles dispensed at the previous visit and count and document number of returned tablets. Document any treatment interruptions, if applicable;
- dispense new bottles of study medication and study ASA with patient instructions;
- remind patient to return with the study medication and study ASA dispensed bottles at their next visit.

9.2.1.4 End of treatment (EOT) visit - amended

Once the Sponsor announces the end of the study, all patients must return to their study site within 4 weeks in order to complete the EOT visit. **Study medication and study ASA will be stopped at this visit**, and it will be left to the discretion of the investigator to initiate any antiplatelet or anticoagulation therapy during the transition of care to the patient's personal physicians.

Likewise, an EOT visit should be performed in those patients who leave the study permanently in spite of any attempts to hold the patient on study observation (see Section 6.3.1).[77]

The following measures/documentations will be performed at the final on-site visit:

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[73] Bullet added with Protocol Amendment 4 (change no. 17)
[74] Bullet added with Protocol Amendment 4 (change no. 12)
[75] Bullet added with Protocol Amendment 4 (change no. 19)
[76] Prior to Protocol Amendment 4, this was "perform ABI (or TBI for non-compressible tibial arteries)" (change no. 5).
[77] Wording revised with Protocol Amendment 4 (change no. 17)

- check for the occurrence of study efficacy and safety outcome events since the last study visit and obtain all supportive information required to complete assessment of these outcome events;
- check for the occurrence of AEs/SAEs since the last study visit (for events exempted from AE/SAE reporting, see Section 9.6.1.3);
- documentation of any changes in concomitant medication since the last study visit;
- assess the patient's PAD Symptom Status;[78]
- QoL assessment with EQ-5D (questionnaires should be completed before the other visit procedures);
- Walking Impairment Questionnaire (questionnaires should be completed before the other visit procedures);
- assess vital signs (blood pressure, pulse rate);[79]
- perform ABI (or TBI);[80]
- collect study medication and study ASA bottles dispensed at the previous visit and count and document number of returned tablets. Document any treatment interruptions, if applicable;
- arrangement of final post-study treatment follow-up phone call.

9.2.1.5 Post-study treatment follow-up visit (PS-FU): one month post-EOT (± 1 week)

Patients will be contacted **by telephone** one month after the EOT visit to allow for collection of final safety data and patient's vital status at study end.

9.3 Population characteristics

9.3.1 Demographics

The following demographic data will be recorded in the eCRF at the screening visit:

- age,
- sex,
- race/ethnicity,
- body weight (kg),
- body height (cm),
- calculated BMI.

78 Bullet added with Protocol Amendment 4 (change no. 12)
79 Bullet moved with Protocol Amendmend 4 (change no. 17)
80 Prior to Protocol Amendment 4, this was "perform ABI (or TBI for non-compressible tibial arteries)" (change no. 5).

9.3.2 Medical history

Medical history findings (i.e., previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator at the screening visit:

- not pertaining to the study indication,
- start before signing of the informed consent,
- considered relevant for the patient's study eligibility.

Special attention must be paid to the PAD-related medical history:

- PAD-related and cardiovascular disease history (MI, angina, intermittent claudication, diabetes, renal dysfunction, heart failure, pacemaker, defibrillator, TIA, stroke, hypertension, etc.);
- PAD-related and cardiovascular surgical and endovascular disease history (coronary percutaneous transluminal coronary angioplasty, atherectomy, PCI, coronary artery bypass graft, peripheral artery bypass surgery, peripheral percutaneous transluminal angioplasty, limb or foot amputation, etc.);
- Medical history of bleeding risk and bleeding (liver diseases, gastrointestinal diseases with bleeding, erosions, ulceration, obstruction, perforation; previous bleeding requiring transfusion, etc.).

Instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.3.3 Definition of qualifying revascularization procedure - amended

[81]For the purposes of the current study, the qualifying revascularization procedure (surgical or endovascular) must include a technically successful procedure distal to the external iliac artery in the past 10 days, and hemostasis must be assured.

Patients under consideration for this trial may have a treatment plan that focuses on a single procedure or staged procedures where not all revascularizations will necessarily be completed at one time. Preferably, the qualifying revascularization should be the last planned procedure.

Surgical procedure: open surgical procedures in the lower extremity for PAD. This can include a variety of procedures, bypass conduit materials, and extra-anatomic operations.

Endovascular procedure: catheter-based procedures and hybrid procedures (those procedures involving aspects of both endovascular and surgical revascularizations) for PAD.

The details about the qualifying revascularization procedure will be recorded at the randomization visit in the eCRF.

Successful procedure: the qualifying revascularization (regardless of type of procedure) procedure must be deemed technically successful by meeting the following criteria:

- technical success of the procedure with no immediate plan for re-intervention and per the investigator's discretion, the patient can safely be placed on an anticoagulant at the time of randomization;

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81 Section revised with Protocol Amendment 4 (change no. 4, 6, 7, 14 and 17) and Protocol Amendment 5 (see change no. 4).

- demonstrated graft or vascular patency of the qualifying revascularization procedure prior to randomization. Graft or vascular patency is at the discretion of the investigator and can be demonstrated by a variety of means including imaging, hemodynamic and/or physical findings.

Sites may be required to submit source documents from the qualifying revascularization procedure for central data verification. [82]

9.4 Efficacy

9.4.1 Assessments and procedures at occurrence of primary efficacy events - amended

In addition to the interviews performed during the regular on-site visits, all study patients are requested to inform the site as soon as possible if they have been hospitalized (regardless of reason) or have experienced other significant adverse medical events in order to ensure timely identification of potential study efficacy outcome events and bleeding events.

The analysis of study efficacy outcome events will be based on events as adjudicated by the ICAC. Thus, the occurrence of study efficacy outcome events must be reported on Outcome/CV Event reporting forms, as described in the Endpoint Event Site Manual[83], and will undergo adjudication by the ICAC. All potential coronary ischemic events, cerebrovascular events and peripheral ischemic events should also be reported on the Outcome/CV Event reporting forms.[84]

The following events will be assessed for primary efficacy (for event definition see Section 9.4.2):

- MI,
- Ischemic stroke,
- CV death,
- ALI,
- Major amputation due to a vascular etiology.

Please note that these study efficacy outcome in addition to bleeding events are exempted from AE/SAE reporting (see Section 9.6.1.3.3).

In addition to investigator-identified study efficacy outcome and bleeding events, safety data will be reviewed regularly for potential major vascular thrombotic events. In particular, Medical Dictionary for Regulatory Activities (MedDRA) preferred terms assigned to investigator-reported AEs will be screened for potential study efficacy outcome and bleeding events and investigators may then be asked to further investigate whether or not a study efficacy outcome or bleeding event occurred and potentially initiate the outcomes reporting process.

Study efficacy outcome events will be continuously collected from signing of the ICF to study end (including the post-study treatment follow-up call).

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82 Sentence added with Protocol Amendment 5 (change no. 6).
83 Sentence revised with Protocol Amendment 5 (change no. 7).
84 Sentence revised with Protocol Amendment 4 (change no. 23).

9.4.2 Definition of study efficacy outcome events

[85]The following definitions are provided for the purposes of this study:

Myocardial infarction (MI): the definition of acute MI is based on the evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia, using the universal MI definition [Thygesen et al. 2012].

Ischemic stroke: the definition of ischemic stroke will be an acute episode of neurological dysfunction caused by focal or global brain vascular injury and includes all strokes that are not of a primary hemorrhagic etiology. This includes fatal and non-fatal strokes.

Cardiovascular (CV) death: all deaths will be assumed CV in nature unless a non-CV cause can be clearly shown.

Acute limb ischemia (ALI): for the current study, ALI is defined as clinical history and presentation consistent with a sudden significant worsening of limb perfusion requiring hospitalization and

- a new pulse deficit with associated rest pain, pallor, paresthesia, or paralysis and either
  - confirmation of arterial obstruction by imaging, limb hemodynamics, intraoperative findings, or pathological evaluation

OR

  - requiring thrombolysis, thrombectomy, or urgent revascularization.

Major amputation due to a vascular etiology: for the current study, this is operationally defined as above-the-ankle amputation that is:

- non-traumatic

AND

- due to a vascular etiology which includes worsening perfusion of the limb but excludes foot sepsis as the primary indication for amputation.

Detailed definitions for these efficacy outcomes are provided in a separate ICAC charter.

9.4.3 Efficacy variables

9.4.3.1 Primary efficacy variable

The primary efficacy outcome of the study is a composite endpoint consisting of:

- the time from randomization to the first occurrence of any component of the following major thrombotic vascular events: MI, ischemic stroke, CV death, ALI, and major amputation due to a vascular etiology.

9.4.3.2 Secondary efficacy variables - amended

The secondary efficacy variables of the 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;

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85 Paragraphs about ischemic stroke, acute limb ischemia, and major amputation due to a vascular etiology revised with Protocol Amendment 4 (change no. 24).

- 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);[86]
- 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 venous thromboembolic (VTE) events;

9.4.3.3 Other efficacy variables - amended

Other efficacy variables of the study are:

- time from randomization to the first occurrence of all subsequent limb revascularizations of a lower extremity that were not planned or considered as part of the initial treatment plan at the time of randomization;[87]
- time from randomization to the first occurrence of above ankle amputation of the index leg or major re-intervention (e.g., new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis);
- time from randomization to the first occurrence of all-cause amputations;
- patient reported outcomes using disease and non-disease specific questionnaires (EQ-5D and WIQ)
- serial changes in limb hemodynamics (ABI/TBI).[88]

9.5 Pharmacokinetics / pharmacodynamics

No pharmacokinetic/pharmacodynamic evaluation will be performed.

9.6 Safety

9.6.1 Adverse events

Introductory note: Due to the broad knowledge about the safety of rivaroxaban based on the comprehensive clinical and post-marketing safety databases available to date, rules for recording and expedited reporting of AEs/SAEs will follow a targeted approach[89] in order to

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86 Bullet revised with Protocol Amendment 4 (change no. 8) and Protocol Amendment 5 (change no. 2).

87 Bullet revised with Protocol Amendment 4 (change no. 8).

88 Bullet added with Protocol Amendment 4 (change no. 13).

89 Principles of targeted safety data collection are laid down in the FDA Draft Guidance for Industry "Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post approval Clinical Investigations" (February 2012)

facilitate the study documentation. The exemptions from AE/SAE documentation and SAE reporting are described in Section 9.6.1.3.2 and Section 9.6.1.3.3.

9.6.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as an AE (however, the condition for which the surgery is required may still be considered an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g., physical examination findings, symptoms, diseases, laboratory, ECG.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g., allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death.

b. Is life-threatening.

   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   – *the admission results in a hospital stay of less than 12 hours*

   – *the admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)*

   – *the admission is not associated with an AE (e.g., social hospitalization for purposes of respite care).*

   However, it should be noted that invasive treatment during any hospitalization may

fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect.

f. Is another serious or important medical event as judged by the investigator.

9.6.1.2 Classifications for adverse event assessment

All AEs requiring documentation will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the eCRF.

Causality should be assessed as detailed in the eCRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments (e.g., owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no".

An assessment of "no" would include:

1. the existence of a highly likely alternative explanation, e.g., mechanical bleeding at surgical site.

or

2. non-plausibility, e.g., the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer diagnosed a few days after the first drug administration.

An assessment of "yes" indicates that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

– the temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.

– Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Patient's response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.

– Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

– Concomitant medication or treatment: The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.

– Known response pattern for this class of drug: Clinical/preclinical.

– Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event.

– The pharmacology and pharmacokinetics of the study treatment: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual patient's pharmacodynamics should be considered.

9.6.1.2.3 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below. The study treatment action should be recorded as detailed in the eCRF.

- none,
- drug withdrawn,
- drug interrupted,
- not applicable (e.g., study drugs already discontinued),
- unknown.

9.6.1.2.4 Other specific treatment(s) of adverse events

- none,
- remedial drug therapy,
- other non-drug treatment (e.g., surgery, endovascular interventions).

9.6.1.2.5 Outcome

The outcome of the AE is to be documented as follows:

- recovered/resolved,
- recovering/resolving,
- recovered/resolved with sequelae,
- not recovered/not resolved,
- fatal,
- unknown.

9.6.1.2.6 Intensity - amended

[90]The intensity of an AE is to be classified according to the following categories:

- mild,
- moderate,
- severe.

9.6.1.3 Targeted safety data collection

Targeted safety data collection is aimed to improve the value of safety data collected by focusing on patient safety and to concentrate the attention on key data to improve clarity of safety reports.

9.6.1.3.1 Assessment of bleeding events

Bleeding events, which are specific safety outcomes of this study, will be continuously monitored from signing of the ICF until post-study treatment follow-up visit.

All bleeding events will be reported on the designated bleeding reporting forms in the eCRF. Since bleeding events are recorded as safety outcome and the risk profile of rivaroxaban has been established in multiple previous studies, these events are not required to be recorded as an AE/SAE and thus are exempted from SAE reporting.

Bleeding occurring after randomization that is related to the index revascularization procedure (e.g. bleeding requiring an unplanned surgical take-back operation to manage[91]) will also be reported, including details of the management of the bleeding event and any limb complications (e.g., resulting in major amputation or compartment syndrome requiring surgical management). These events will be reviewed by the IDMC on a regular basis and not reported as SAEs.

Potential major bleedings occurring after randomization will undergo adjudication by the ICAC. Major bleeding as adjudicated per TIMI classification is considered the primary safety outcome of the study, but other bleeding types (e.g., based on BARC and ISTH criteria) will also be evaluated as defined in the ICAC charter.

9.6.1.3.1.1 Primary safety outcome - occurrence of major bleeding as per TIMI definition

The primary safety outcome will be major bleeding events according to the TIMI classification.

Additional information on the definition of major bleedings can be found in the ICAC charter.

9.6.1.3.1.2 Secondary safety outcomes

In addition to the TIMI classification, bleeding events will be assessed using the BARC and the ISTH classifications, as defined in the ICAC charter.

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90 This section was added with Protocol Amendment 4 because it was erroneously omitted from the original version (change no. 16).

91 Text revised with Protocol Amendment 4 (change no. 17).

9.6.1.3.2 Assessments and documentation of adverse events – amended

The investigator has to record on the respective eCRF pages all AEs occurring in the period between the signing of the ICF and the end of the follow-up phase (i.e., post-study treatment follow-up visit by phone at 4 weeks after the EOT visit) according to the guidelines outlined in Sections 9.6.1.3.2 and 9.6.1.3.3.[92] After the end of the follow-up phase there is no requirement to actively collect AEs including deaths. In case of permanent discontinuation of study medication, AEs other than outcome events must be reported up to one month after the last dose of study medication intake.

The type of information that should be assessed and recorded by the investigator for each AE requiring documentation is listed in Section 9.6.1.2. "Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s). For all serious adverse events (SAEs), the Sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

In the current study, a targeted approach will be followed for AE/SAE documentation and reporting. Regarding non-serious AEs, this basically means that only

i) non-serious AEs leading to screening failure (pre-randomization),

ii) non-serious AEs leading to permanent discontinuation of study-drug treatment (post-randomization), and

iii) any non-serious AEs of particular concern to the investigator

will be captured on the AE page of the eCRF (but these events do not require further reporting to the Sponsor's pharmacovigilance (PV) department).[93] **Other non-serious AEs will not be collected because of the large available safety database for rivaroxaban.**

The handling of SAEs is described in the following Section 9.6.1.3.3.

9.6.1.3.3 Reporting of serious adverse events and study-specific exemptions - amended

The common definition of SAEs is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

The efficacy and safety outcomes in this study will be collected in the eCRF and regularly monitored by the IDMC during the entire course of the study in a timely adequate manner. Due to this targeted surveillance, no AE documentation and no expedited SAE reporting will be performed for these events. Consequently, they will neither be un-blinded nor reported to regulatory authorities, IECs, or investigators. The IDMC will periodically review and assess all safety data for imbalances in safety outcomes. It is believed that in this way patient safety can continue to be monitored throughout the duration of the trial, along with study integrity. If unexpected safety issues are identified, specific amendments will be implemented.

The following rules should be followed:

1. **Primary and secondary efficacy outcome events** occurring after randomization will not be recorded on the AE page and not be reported as SAEs to Sponsor's PV

[92] Cross-references added by Amendment 4 (change no. 17).
[93] Wording changed by Amendment 4 (change no. 17).

department, but they will be collected on the specific eCRF pages as an efficacy outcome event.

2. **Safety outcome events** (i.e., bleeding events occurring after signing of the ICF) will not be recorded on the AE page and not be reported as SAEs to Sponsor's PV department, but they will be collected on the specific eCRF pages as a safety outcome event. [94]
3. **All other SAEs (including complications of efficacy or safety outcome events)** that fulfill the seriousness criteria provided in Section 9.6.1.1 need to be collected on the eCRF (AE page) and reported as SAEs to the PV department. All SAEs that fulfill SUSAR criteria will be reported to the concerned authorities by expedited means (see Section 9.6.1.4).
4. **Pregnancies** need to be captured and reported to the Sponsor's PV department within 24 hours, even if classified as non-serious (see Section 9.6.2).

Investigator's notification of the Sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (i.e., within 24 hours of the investigator's awareness) all SAEs not exempted from SAE reporting occurring during the observation period to the recipient detailed in the instructions for SAE reporting included in the investigator site file. For this, an AE page in the eCRF as well as the complementary pages provided in the investigator site file must be completed for each SAE.

The investigator is responsible for continuing to follow all SAE reports (whether or not related to study drug) until resolution or until the event is considered chronic and/or stable by the investigator and/or other physician who has the responsibility for the patient's medical care. Follow-up SAE reports will be reported according to the same timelines as initial reports, as soon as new significant information becomes available (in conformity with the Sponsor's PV guidance).

SAEs occurring after the protocol-defined observation period will be processed by the Sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g., SAEs, SUSARs) will be performed by the Sponsor and/or by the investigator according to all applicable regulations and policies.

Notification of the authorities

The processing and reporting of all relevant events (e.g., SAEs, SUSARs) to the authorities will be done by the Sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The Sponsor will inform all investigational sites about reported relevant events (e.g., SUSARs) according to all applicable regulations.

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94 No. 2 changed with Protocol Amendment 5 (change no. 7).

9.6.1.4 Expected adverse events

For this study, the applicable reference document is the most current version of the Investigator's Brochure (IB).

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the Sponsor according to the applicable reference document (IB) and according to all local regulations. All SAEs that fulfill the SUSAR criteria as defined by the International Conference on Harmonization (ICH) E2A Guideline will be reported to the concerned authorities by expedited means.

In compliance with applicable regulations, in the event of a SUSAR, the patient's treatment code will usually be unblinded before reporting to the competent authorities, IECs/IRBs. For reporting to investigators, the treatment blind, if possible, will be kept.

9.6.2 Pregnancies

Pregnancy (and its outcome) in a patient or in the patient's partner need to be captured and reported to Sponsor's PV department within 24 hours even if classified as non-serious. If the pregnancy/outcome of pregnancy fulfills SUSAR criteria, the outcome of the pregnancy will be reported to the concerned authorities by expedited means.

The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported. For a pregnancy in the partner of a male study patient, all efforts will be made to obtain similar information on course and outcome, patient to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

9.6.3 Further safety – amended

In this study, vital signs assessments will be performed at each study visit as further safety measures. Vital signs (systolic and diastolic blood pressure, pulse rate) will be measured either in a supine or sitting position (preferably in the same position per patient) after a minimum of 5 minutes rest.

It is also generally expected that study visit assessments of subjects occurs under the direct supervision of medically qualified personnel such as a physician to determine the need for additional evaluations. It is expected that laboratory surveillance should follow standard of care, tailored to the specific need and clinical indications of the subjects. As part of standard in-hospital, perioperative, and chronic care of such patients with known vascular conditions, repeat and in some cases frequent laboratory testing may be required. Record the relevant laboratory parameters on the corresponding eCRFs.[95]

9.7 Other procedures and variables

9.7.1 European Quality of Life-5 Dimensions Questionnaire - amended

For the quality of life assessment the European Quality of Life-5 Dimensions Questionnaire (EQ-5D) will be used as a standardized measure of health outcomes. The assessment is

[95] Paragraph was added with Protocol Amendment 4 (change no. 19)

applicable to a wide range of health conditions and treatments and it provides a simple descriptive profile and a single index value for health status. The EQ-5D is primarily designed for self-completion by patients.

The EQ-5D will be administered at the randomization visit, and subsequently at each on-site visit.[96]

9.7.2 Walking Impairment Questionnaire - amended

The Walking Impairment Questionnaire (WIQ) is an effective and validated tool to assess the objective improvement or deterioration in the daily walking ability of PAD patients [Nicolai et al. 2009]. Assessments will be performed at the randomization visit, and subsequently at each on-site visit.[97]

9.7.3 Health resource use - amended

[98]Health care resource utilization data related to all efficacy and safety outcomes events referred to as Health Care Resource Utilization (HCRU) will be collected for all patients during the study using the Health Care Resource Utilization form in the eCRF. These may include: hospitalizations (total days length of stay, intensive care unit/cardiac care unit days, ward type), emergency room visits, unscheduled out-patient physician consultations, visits related to bleeding, surgeries, other and selected procedures (inpatient and outpatient), and days off-work. Country-specific cost data may be linked at a later stage.

9.7.4 PAD Symptom Status - amended

[99]The PAD Symptom Status assessment is a graded scale used to assess the severity of chronic PAD. This assessment tool, adapted from the commonly-used Rutherford classification of chronic limb ischemia [Rutherford et al. 1997], categorizes subjects' condition into one of six strata of chronic limb ischemia severity ranging from asymptomatic to tissue loss beyond the digits of the foot. This assessment will be completed by the investigator at the Randomization visit, and subsequently at each on-site visit.

9.8 Appropriateness of procedures / measurements

With the exception of routine laboratory assessments performed at Screening, no invasive procedures are planned for this study. All study visits will be used to collect safety and outcome data that are considered appropriate measures for this event-driven trial (see Section 3.3).

10. Statistical methods and determination of sample size

10.1 General considerations

A general description of the statistical methods is outlined below. A Statistical Analysis Plan (SAP) will be provided in a separate document and will contain a more technical and detailed description of the planned analyses. The core SAP is targeted to be finalized prior to study enrollment. Amendments and/or appendices to the core SAP will provide more details on the

96 Sentence was revised with Protocol Amendment 4 (change no. 17)
97 Sentence was revised with Protocol Amendment 4 (change no. 17)
98 This section was modified with Protocol Amendment 4 (change no. 17).
99 This section was added with Protocol Amendment 4 (change no. 12)

coding guidelines, data-handling, and output tables and figures. These SAP-associated documents are targeted for completion 6 months before the planned interim analysis.

Analyses will be performed using SAS software (SAS Institute Inc., Cary, North Carolina, USA); the version used will be specified in the SAP.

10.2 Analysis sets

The **efficacy analyses** will be based on the intent-to-treat (ITT) population, which comprises all randomized patients. In the ICH E9 guideline this is also termed the Full Analysis Set. Patients will be categorized to the group to which they were assigned by the IxRS; i.e., they will be analyzed as randomized.

The **safety analyses** will be based upon the safety analysis set, which comprises all treated patients, i.e., randomized patients who received at least one dose of study drug. For the purpose of safety analyses, patients 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, patients will be analyzed for safety as actually treated.

10.3 Variables and planned statistical analyses

10.3.1 Variables

The efficacy outcome variables of this study are defined in Section 9.4.3.1 (primary efficacy variable), Section 9.4.3.2 (secondary efficacy variables), and Section 9.4.3.3 (other efficacy variables). The ITT data scope (primary data scope for the efficacy analyses) will include all outcome events observed from randomization until the efficacy cut-off date. The follow-up period for each patient will be as long and complete as possible.

The safety outcomes of this study are defined in Section 9.6.1.3. The on-treatment data scope (primary data scope for the assessments of the aforementioned safety variables) will include all outcome events observed from randomization until 2 days following permanent discontinuation of the study drug.

10.3.2 Planned subgroups

Subgroup analyses based on demographic characteristics (such as age, sex, race, etc.) and baseline randomization stratum are planned. Additional subgroups will be specified in the SAP.

10.3.3 Statistical and analytical plans

10.3.3.1 Analysis of the primary efficacy variable

The primary efficacy 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) including CV death, MI, ischemic stroke, major amputation, and ALI, using the ITT principle (i.e., patients as randomized [Full Analysis Set] considering all events until the efficacy cut-off date).

The null hypothesis will be:

> $H_{0,\,PE}$: $S_R(t) = S_A(t)$ for all time points $t \geq 0$, (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 $t \geq 0$, and $S_R(t) \geq S_A(t)$ for all time points $t \geq 0$, (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 use of clopidogrel ((i.) surgical vs. (ii.) endovascular with clopidogrel vs. (iii.) endovascular without clopidogrel) with treatment as 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 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 RR reduction will be estimated using a Cox proportional hazards model, stratified by type of procedure and use of clopidogrel, 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 model.

10.3.3.2 Analysis of the secondary and other efficacy variables

The secondary efficacy variables are provided in Section 9.4.3.2 and the other efficacy variables are presented in Section 9.4.3.3.

The secondary efficacy variables will be analyzed similarly to the primary efficacy variable.

If the superiority of rivaroxaban for the primary variable is declared, the secondary efficacy variables will be tested in the sequential order as listed in in Section 9.4.3.2.

The other efficacy variables will be analyzed similarly to the primary efficacy variables except for the patient reported outcomes and considered exploratory.

10.3.3.3 Analysis of safety outcomes and regular adverse events

Time to the first occurrence of the primary safety outcome (i.e., TIMI major bleeding) will be compared using a Cox proportional hazards model stratified by type of procedure and clopidogrel use with treatment group as a covariate. The analysis will be conducted in the safety analysis set and for the on-treatment data scope. The other time-to-event safety outcomes will be analyzed similarly.

Adverse events reported as per study-specific rules for event exemption (Section 9.6.1.3) will be analyzed by MedDRA system organ class and preferred term level using tabulated summaries with absolute and relative frequencies.

10.3.3.4 Analysis of subgroups

Analyses for the primary efficacy and safety outcomes for the subgroups as listed in Section 10.3.2 will be performed based on the same analysis sets and data scopes as in the main analyses, and presented descriptively. Homogeneity of treatment effect in subgroups, both in magnitude and direction, will be assessed.

10.3.3.5 Handling of missing data

All efforts will be made to collect complete data for all patients randomized in this study including visits by telephone contact. Patients 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 to be the middle date within the period that the event is known to have occurred, e.g., if the event is known to have occurred in the first week of a month, then the date in the middle of that week will be used; if no information is known then the date in the middle of the plausible time period will be used, based on the last contact with the patient prior to the event and the date of contact when information about the event was known.

If a patient experiences a fatal event that is not part of a specific endpoint under analysis, the patient will be considered as having been censored at the earlier date of efficacy cut-off or the time of death. If a patient is lost to follow-up or has withdrawn consent and has not experienced any endpoint events under analysis, the patient will be counted as censored at the last contact date prior to the date of efficacy cut-off, with complete information of the endpoint being analyzed (e.g., for analysis of the primary endpoint, information regarding all components of the primary endpoint need to available at the contact date).

10.4 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) for rivaroxaban 2.5 mg bid plus study ASA 100 mg od vs. placebo plus study ASA 100 mg od is HR=0.8;
- 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% in the 1st year, 8% in the 2nd year, 12% in the 3rd year (4% 1st half + 8% 2nd half), 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% in the 1st 6 months, 30% in the 2nd 6 months, and 55% in the 3rd 6 months) and 2 years of follow-up from last patient-randomized until the efficacy cut-off date.

The event rates used for this sample size estimation are extrapolated from recent studies such as the TRA2^{o}P-TIMI 50 trial. Based on the TRA2^{o}P-TIMI 50 study, both the CV and limb events are estimated at an annualized rate of approximately 4% each, with both CV and limb events being higher in those patients who had a history of prior peripheral revascularization procedure [Bonaca et al. 2013]. It is assumed that, given the acuity of the population based on underlying symptoms and CLI presentation, the proximity to the revascularization procedure, and the fact that the patients in this study will all have a revascularization procedure, the short

and intermediate term events would be considerably higher. Also these CV and limb events are generally considered non-overlapping and non-competing.

Inherently, the number of patients enrolled may be adjusted based on the observed overall event rate of the primary efficacy outcomes during the study. Sample size estimation was based on PASS 11[100] [Hintze 2011].

10.5 Planned interim analyses

The 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 have accrued. Based on that analysis, the study may be stopped early, if there is overwhelming superiority of rivaroxaban ($p<0.001$, 2-sided) for primary efficacy endpoint (following the Haybittle-Peto approach). Due to the conservative amount of alpha spent at interim, no alpha adjustment will be made for the final efficacy analyses [Haybittle 1971].

Also, secondary efficacy and safety will be considered. The study will be stopped early if the totality of data suggests an overwhelming benefit of rivaroxaban added to ASA over ASA alone. No formal boundaries have been set for terminating the study for safety reasons; but clear, consistent, and persistent evidence of net harm that overwhelms any benefit should be apparent through periodic assessment by the IDMC.

Details on the modalities of the interim analyses and decision rules will be specified in the IDMC charter.

11. Data handling and quality assurance

11.1 Data recording

[101]Data required according to this protocol will be recorded by trained investigational site personnel via data entry into the internet based validated EDC software system RAVE from Medidata Solutions. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All study personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

Sites must implement processes to ensure that all data entered into the eCRF are supported by source documentation. A source document checklist will be used at the site to identify the

100 Reference added with Protocol Amendment 4 (change no. 17)
101 Section revised with Protocol Amendment 4 (change no. 17).

source data for all data points collected, in accordance with the latest version of the protocol and study agreements[102].

Data recorded from screening failures

Data of 'only screened patients' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, the following data should be recorded in the eCRF:

- demographic information (patient number; year of birth / age; sex; race / ethnicity),
- date of informed consent,
- reason for premature discontinuation,
- date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the eCRF in addition to the data specified above:

- all information about the SAE,
- all information related to the SAE such as:
  - concomitant medication,
  - medical history,
  - other information needed for SAE complementary page.

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

Generally, the sponsor/designee will monitor the site activity to verify that the:

- data are authentic, accurate, and complete,
- safety and rights of patients are being protected,
- study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol),
- any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

The data collection tool for this study will be a validated electronic system called Medidata RAVE. Patient data necessary for analysis and reporting will be entered / transmitted into a

[102] Sentence deleted with Protocol Amendment 4 (change no. 16).

validated database or data system (e.g., Tools for syntactic corpus analysis [TOSCA]; SAS). Clinical data management will be performed in accordance with the applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on the eCRF as well as for data from other sources (e.g. IxRS, ICAC, Laboratory).
For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

11.4 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.5 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g., relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof) at any time, which may be due but not limited to the following reasons:

- if risk-benefit ratio becomes unacceptable owing to, for example,
  - safety findings from this study (e.g., SAEs),
  - results of any interim analysis,
  - results of the review by the IDMC,
  - results of parallel clinical studies,
- if the study conduct (e.g., recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the study within a reasonable time frame.

The investigator has the right to close his/her center at any time. In this case, it may be explored whether patients can still be further followed-up for outcome events and vital status or whether patients could be switched to another investigational site.

For any of the above closures, the following applies:

- closures should occur only after consultation between involved parties. Final decision on the closure must be in writing,
- all affected institutions (e.g., IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law,
- all study materials (except documentation that has to remain stored at site) must be returned to the Sponsor. The investigator will retain all other documents until notification is given by the Sponsor for destruction,
- in the event of a partial study closure, ongoing patients, including those in post study follow-up, must be taken care of in an ethical manner.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

13.1.1 Investigators

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained, and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g., health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13.1.2 Study personnel

Study personnel relevant for the centers will be available in each center's investigator site file.

13.1.3 External data evaluation bodies

Four study committees will be established in order to ensure a proper study conduct according to the state of the art as well as independent, consistent, and high-quality data review. Separate charters will be prepared for all study committees overseeing the study including the personnel, responsibilities, procedures, and meeting frequencies. Generally, the committees are:

Executive Committee (EC)

The EC will consist of academic and sponsor members. The EC has the final decision responsibility and will provide scientific input into the overall trial design and specific trial methodologies. In addition, the EC will contribute to the development of the statistical analysis plans and will serve as the publication committee. It will be actively engaged in discussions with regulatory authorities, will be responsible for identifying and populating the key trial committees and will actively participate in site selection. The EC will meet regularly during the study conduct and provide key input into ongoing trial operations, will work with the Sponsor and CRO/ARO to identify issues in trial conduct with a focus on resolution of those issues. Communication with trial committees, national lead investigators, and trial sites will be overseen by the EC. Likewise, any recommendations in trial conduct from the IDMC or changes in the protocol will be overseen by the EC.

International Steering Committee (ISC)

The International Steering Committee (ISC) will consist of the 2 co-principal investigators, National Lead Investigators from all countries, and sponsor representatives. The ISC will be responsible for all scientific aspects of the study and will ensure that study execution and management of the study are of the highest quality. The ISC will convene regularly to discuss and report on ongoing supervision of the study.

Independent Data Monitoring Committee (IDMC)

The primary role of the IDMC is to ensure the safety of the patients in the ongoing study. The IDMC will comprise a chair, co-chair, and members who have recognized expertise in clinical trials, neurologic or cardiovascular disease, and/or biostatistics; and who are not members of the ISC, or involved as investigators or otherwise in the trial.

Independent Central Adjudication Committee (ICAC)

The Independent Central Adjudication Committee (ICAC) will comprise of members with appropriate clinical and methodological expertise, blinded to study medication assignment, who will be responsible for adjudication and classification of outcome events in the study.

13.2 Funding and financial disclosure

Funding

This study will be funded by the Sponsor Bayer HealthCare AG[103] and Janssen Pharmaceuticals Inc.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration

[103] Text revised with Protocol Amendment 4 (change no. 17).

of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g., IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the EC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated patient information sheet and ICF provided by the sponsor. A sample patient information and ICF is provided as a document separate to this protocol.

Based on this patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient, prior to his/her entry into the study (i.e., before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each patient will be informed about the following aspects of premature withdrawal:

- each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient's consent covers end-of-study examinations as specified in the visit description described in Section 9.2.1.4 to be conducted after withdrawal of consent.
- The patient's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Patient-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine, or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The patient has the right to object to the generation and processing of this post-withdrawal data. For this, he/she needs to

sign a corresponding declaration of objection; alternatively, the patient's oral objection may be documented in the patient's source data.

Each patient will have ample time and opportunity to ask questions.

Only if the patient voluntarily agrees to sign the ICF and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The patient will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient´s clinical record must clearly show that informed consent was obtained prior to these procedures.

If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

The ICF and any other written information provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and/or the written ICF. The investigator will inform the patient of changes in a timely manner and will ask the patient to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

The results of the VOYAGER PAD study will be published, irrespective of the findings. The primary results will be prepared for publication and submitted to a respective journal in a timely fashion following final data lock and delivery of all validated tables, figures and listings. At the conclusion of the VOYAGER PAD trial, the EC will serve as the main core of a Publications Committee and will manage the publication of the primary study results and subsequent analyses. The Publications Committee will review all manuscript proposals for scientific merit and approve the authorship and content of all proposals. Journal papers produced by the EC will comply with the guidelines set forth by the uniform requirements for manuscripts submitted to biomedical journals, drawn up by the International Committee of Medical Journal Editors, see http://www.icmje.org/.

The EC will provide the final draft version for publication to the sponsor for review; the EC will maintain the authority of final approval of the manuscript to submit for publication. The sponsor will have a period of up to 30 days for review and comment prior to submission of any manuscripts for publication.

The EC will co-ordinate the timing and authorship of derived publications referring to data from this study to ensure that secondary publications do not jeopardize the primary publications from this study.

13.6 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the eCRF, and if the patient name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.
If the results of the study are published, the patient's identity will remain confidential.
The investigator will maintain a list to enable patients to be identified.

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[104] Reference added with Protocol Amendment 4 (change no. 17)

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[105] Reference added with Protocol Amendment 4 (change no. 12)

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15. Protocol amendments

15.1 Amendment 4

15.1.1 Overview of changes to the study

Amendment 4 is the first global amendment to the original clinical study protocol 17454 Version 1.0, dated 23 March 2015.

Change 1: Administrative change

Rationale: The Sponsor's study medical expert has changed. Instead of PPD PPD has taken over this task.

Section affected include:

- Title page

Change 2: The timing from randomization from the qualifying revascularization has changed from no later than 7 days to no later than 10 days

Rationale: It has been recognized that many subjects are discharged either the same day or the following day after their qualifying revascularization. In consideration of the difficulty of having subjects travel to the clinical research site so quickly after a revascularization procedure, the timing from the qualifying revascularization to randomization has been extended from 7 days to 10 days to facilitate enrollment.

Sections affected include:

- Section 2, Synopsis (Methodology)
- Section 5, Study design (also Figure 5-1)
- Section 6.1, Inclusion criteria (criterion 3)
- Section 9.1, Tabular schedule of evaluation (Table 9-1, footnote a)
- Section 9.2.1.2, Randomization visit (RxV)

Change 3: The timing of screening was changed from up to 7 days after the qualifying revascularization to up to 30 days before, to up to 10 days after the qualifying revascularization (-30 days to +10 days)

Rationale: This change provides the opportunity to consent subjects prior to the qualifying revascularization procedure. It is felt to be more beneficial for the consent process and enrollment to be able to approach subjects pre-operatively. This will also provide more of an opportunity to complete the required eligibility procedures that may not have been performed prior to the revascularization.

Sections affected include:

- Section 2, Synopsis (Methodology)
- Section 5, Study design
- Section 9.1, Tabular schedule of evaluation (Table 9-1, footnote a)

- Section 9.2.1.1, Screening visit (ScV)

Change 4: The anatomic location of eligible PAD was changed from "infra-inguinal" to "distal to the external iliac artery".

Rationale: "Infra-inguinal" was interpreted as distal to the common femoral artery. This change allows isolated common femoral procedures which has been recognized to include common practice patterns in certain geographic areas. The inclusion of this anatomic location is also felt to potentially benefit from study intervention and will contribute to enrollment of the study.

Sections affected include:

- Section 2, Synopsis (Diagnosis and main criteria for inclusion/exclusion)
- Definition of medical terms (Endovascular / Surgical procedure)
- Section 6.1, Inclusion criteria (criteria 2b and 3)
- Section 9.3.3, Definition of qualifying revascularization procedure

Change 5: The ABI/TBI inclusion criterion was clarified.

Rationale: Qualifying symptoms and evidence of anatomic disease is specific to the leg undergoing revascularization. ABI/TBI criterion can be from either leg. A qualifying ABI or TBI from either leg can qualify a patient for the study, as this is felt to be sufficient to identify subjects with clinically significant PAD but also recognizes the fact that there is not a perfect correlation between ABI/TBI severity and symptom severity. There is no longer the requirement for non-compressible ABI result to allow TBI assessment, as this recognizes the scenario whereby the ABI rises in the setting of progressive arterial calcification, prior to becoming non-compressible.

Sections affected include:

- Section 2, Synopsis (Diagnosis and main criteria for inclusion/exclusion)
- Section 6.1, Inclusion criteria (criterion 2c)
- Section 9.1, Tabular schedule of evaluation (Table 9-1, footnote g)
- Section 9.2.1.1, Screening (Visit) (ScV)
- Section 9.2.1.3, Treatment phase: Regular study visits from Visit 1 onwards
- Section 9.2.1.4, End of treatment (EOT) visit

Change 6: The definition of qualifying revascularization was clarified and altered.

Rationale: Formerly was described as the last planned procedure if multiple procedures are performed on one leg, and silent on bilateral procedures. Changed to subjects are eligible to enroll after any qualifying revascularization on either leg; recommending (not requiring) last planned procedure if multiple procedures are planned. The change made to the 'Definitions of medical terms' simplifies the definition and consolidates the description of determinants of the qualifying revascularization into one section 9.3.3. This change is also felt to eliminate

ambiguity of the stated preference for enrollment after the last planned procedure in the setting of a staged revascularization treatment plan and the prior statement of defining the index leg as the most symptomatic leg. It is recognized that staged treatment plans often address the most severe lesions first and the less severe lesions with subsequent procedures.

Sections affected include:

- Definition of medical terms, Qualifying revascularization
- Section 9.1, Tabular schedule of evaluations (Table 9-1, footnote g)
- Section 9.3.3, Definition of qualifying revascularization procedure

Change 7: Subjects with prior revascularization on the index leg within 8 weeks of the qualifying revascularization were to be excluded from the study. The timeframe was changed to 10 days of the qualifying revascularization to accommodate staged treatment plans. The definition of the index leg was also simplified to reflect changes in the protocol regarding staged revascularization treatment plans and the recognized difficulty in identifying the most symptomatic leg in some cases.

Rationale: To be consistent with Change 2 and Change 6.

Sections affected include:

- Section 2, Synopsis (Diagnosis and main criteria for inclusion/exclusion)
- Definition of medical terms (Index leg)
- Section 6.2, Exclusion criteria (criterion 3)
- Section 9.3.3, Definition of qualifying revascularization procedure

Change 8: The secondary and exploratory efficacy endpoints dealing with revascularization was revised to specify that the endpoint is only for subsequent revascularizations that were not planned or considered as part of the treatment plan at the time of randomization.

Rationale: To be consistent with change 6, this was further clarified to clearly delineate planned and staged subsequent revascularizations from unplanned revascularizations on the index leg for the purposes of analysis of a secondary efficacy endpoint.

Sections affected include:

- Section 2, Synopsis (Study objective[s] and Primary and secondary variable[s])
- Section 4, Study objectives
- Section 9.4.3.2, Secondary efficacy variables
- Section 9.4.3.3, Other efficacy variables

Change 9: The guidance on DAPT following the qualifying revascularization was revised to allow the use of >30 days, or >60 days in cases of labeled indication for a device, if the investigator determines that a medical need arises that warrants a longer course of clopidogrel therapy.

Rationale: This allows the investigator to increase the duration of DAPT if the clinical need arises during the course of initial DAPT in select cases by documenting this justification in the medical record. The aim here is to allow for investigator discretion and reflect real world practice without having this being a protocol violation.

Sections affected include:

- Section 8.1, Prior and concomitant therapy

Change 10: The timeframe of the laboratory tests required to verify eligibility criteria (creatinine/eGFR) was changed from within 7 days prior to the qualifying revascularization to within 30 days prior to the qualifying revascularization.

Rationale: This was changed to be more consistent with practice patterns.

Sections affected include:

- Section 9.1, Tabular schedule of evaluations (Table 9-1, footnote c)
- Section 9.2.1.1, Screening visit (ScV)

Change 11: The rules for study drug interruption due to prohibited medications were clarified.

Rationale: To correct conflicting information as well as to provide additional guidance on concomitant use of prohibited medications in the interest of subject safety.

Sections affected include:

- Section 7.4.4, Guidance for the treatment of subjects who develop an acute coronary syndrome and those who require percutaneous coronary intervention with stenting

Change 12: The assessment of PAD Symptom Status was added to the randomization and all follow-up visits

Rationale: To correct an omission of the original protocol.

Sections affected include:

- Section 9.1, Tabular schedule of evaluations (Table 9-1)
- Section 9.2.1.2, Randomization visit (RxV)
- Section 9.2.1.3, Treatment phase: Regular study visits from Visit 1 onwards
- Section 9.2.1.4, End of treatment (EOT) visit
- Section 9.7.4, PAD Symptom Status (*new section*)
- Section 14, Reference list

Change 13: Serial changes in limb hemodynamics (ABI/TBI) was added as an exploratory endpoint.

Rationale: To describe an additional planned analysis of study data.

Section affected include:

- Section 9.4.3.3, Other efficacy variables

Change 14: The description of "successful procedure" was revised.

Rationale: Definition further clarified to reflect what is expected to meet this criteria.

Section affected include:

- Section 9.3.3, Definition of qualifying revascularization procedure

Change 15: The following was added as an exclusion criterion: "Patients with major tissue loss (defined as significant ulceration/gangrene proximal to the metatarsal heads, i.e. heel or midfoot) in either leg" .The previous protocol excluded major tissue loss of the index leg in exclusion criterion #1. The reference to "major tissue loss" in exclusion criterion #1 was removed and incorporated into the new, broadened exclusion criterion (#5) which now excludes major tissue loss of either leg.

Rationale: These patients are felt to have an end stage condition that is beyond the point of deriving benefit from study intervention.

Section affected include:

- Synopsis (Diagnosis and main criteria for inclusion/exclusion)
- Section 6.2, Exclusion criteria (criteria 1 and 5)

Change 16: Standard text from the protocol template was added / deleted

Rationale: The standard text was erroneously omitted from the original protocol or standard text was erroneously added twice in the same section or added to the wrong section.

Section affected include:

- Section 3.4, Background (*sentence added*)
- Section 6.3.1, Discontinuation and withdrawal (*sentence added*)
- Section 7.4.1 Dose Modification (sentence deleted and added to Section 3.4)
- Section 9.6.1.2.6, Intensity (*section added*)
- Section 11.1, Data recording (*sentence deleted*)

Change 17: Minor clarifications and edits for consistency were made.

Rationale: These minor changes were made to ensure consistency and clarity throughout the document.

Section affected include:

- Section 2, Synopsis (Study objectives, Background treatment, Diagnosis and main criteria for inclusion / exclusion, Methodology)
- Definition of medical terms
- Section 4, Study objectives
- Section 16.2, Exclusion criteria (criteria 7, 12, 23)
- Section 7.1, Treatment to be administered
- Section 7.4, Dosage and administration
- Section 7.4.3, Guidance for the treatment of subjects who require coronary artery bypass graft (CABG) surgery
- Section 7.4.1, Dose modification
- Section 7.4.4, Guidance for the treatment of subjects who develop an acute coronary syndrome and those who require percutaneous coronary intervention with stenting
- Section 8.1, Prior and concomitant therapy
- Section 9.1, Tabular schedule of evaluations (Table 9-1, abbreviations and footnotes c and f)
- Section 9.2.1.1, Screening visit (ScV)
- Section 9.2.1.2, Randomization visit (RxV)
- Section 9.2.1.3 Treatment phase: Regular study visits from Visit 1 onwards
- Section 9.2.1.4, End of treatment (EOT) visit
- Section 9.3.3, Definition of qualifying revascularization
- Section 9.6.1.3.1, Assessment of bleeding events
- Section 9.6.1.3.2, Assessment and documentation of adverse events
- Section 9.7.1, European Quality of Life-5 Dimensions Questionnaires
- Section 9.7.2, Walking Impairment Questionnaire
- Section 9.7.3, Health resource use
- Section 13.2, Funding and financial disclosure
- ´Section 10.4, Determination of sample size
- Section 11.1, Data Recording
- Section 14, Reference list

Change 18: "Breast feeding" as additional exclusion criterion added

Rationale: This exclusion criterion was added to be consistent with the package labelling of study medications.

Section affected include:

- Section 6.2 Exclusion criteria (criterion 25)

Change 19: Documentation of laboratory evaluations

Rationale: The request for a documentation of the laboratory evaluations was added to reflect the standard medical care. This change will also add uniformity of data collection across all sites, as rare countries have regulatory bodies that have required the additional collection of laboratory evaluations for safety monitoring. Since these laboratory evaluations are not mandated in the product labeling of rivaroxaban, the intent was to not mandate these procedures to maintain consistency with the product labeling. This may also serve to demonstrate that the study population is receiving optimal medical care for cardiac risk factor modification. Local reference ranges will be added at the site level.

Section affected include:

- Section 9.2.1.2, Randomization visit (RxV)
- Section 9.2.1.3, Treatment phase: Regular study visits from Visit 1 onwards
- Section 9.6.3, Further safety

Change 20: Further clarification of definition of inclusion criteria for PAD

Rationale: This change includes 3 justifications:

a) "Atherosclerotic" was added to clarify that the etiology of PAD should be atherosclerotic- related rather than an alternative etiology that may respond differently to this treatment
b) "Occlusive" was removed and the wording "peripheral" was added for consistency and further clarity. The word "arterial" was changed to "artery" for consistency.
c) The timeframe of prior ABI/TBI testing for inclusion has been extended to "12 months" to more align with practice patterns and is not felt to impact the patient population being enrolled.

Section affected include:

- Section 2, Synopsis (Diagnosis and main criteria for inclusion/exclusion)
- Section 6.1, Inclusion criteria

Change 21: Inclusion criteria 7 was modified by removing the requirement of men to use contraception

Rationale: This is consistent with the product labeling and existing data demonstrating no known genotoxic effects of rivaroxaban.

Based on information in the IB for Rivaroxaban, contraception is not required for male subjects enrolled in the study nor their female partners. The language for this inclusion criteria for female subjects of child-bearing potential will be modified to be consistent with other similar rivaroxaban studies presently enrolling.

The language for Change 21 and Inclusion criteria 7 was changed to the following: 'Women of reproductive potential must agree to use adequate contraception* when sexually active. This applies for the time period between signing of the informed consent form (ICF) to the last administration of study drug.'

Section affected include:

- Section 6.1, Inclusion criteria (criterion 7)

Change 22: Further clarification of prohibited therapies

Rationale: This change includes 4 justifications:

a) The use of prasugrel and ticagrelor was specifically added to the list of prohibited antiplatelet therapy in the interest of patients safety
b) The wording for "heparins" added for completeness and consistency
c) The sentence *"Study medication shall be discontinued in patients who develop any condition which requires permanent or long term anticoagulation (e.g., DVT, atrial fibrillation)"* was removed as it was felt to be redundant and removed for clarity and consistency
d) The sentence *"After PCI or CABG, treatment with DAPT should be considered for at least 48 hours."* was removed as it was felt to have been placed in the protocol in error.

Section affected include:

- Section 8.1, Prior and concomitant therapy

Change 23: Further guidance on reporting of clinical outcome events

Rationale: A sentence was added to inform investigators of the expectation that any clinical outcome event that could possibly be considered as such an event should also be reported for consideration by the ICAC.

Section affected include:

- Section 9.4.1, Assessments and procedures at occurrence of primary efficacy events

Change 24: Further clarification of definition of study efficacy outcome events

Rationale: Minor changes were made to event definitions to be consistent with the outcome event definitions in the adjudication charter.

Section affected include:

- Section 9.4.2, Definition of study efficacy outcome events

Change 25: Deletion of Appendix 16.1

Rationale: The decision was made to not pursue the duplex ultrasound substudy.

Section affected include:

- Section 9.2.1.3, Treatment phase: Regular study visit from Visit 1 onwards
- Section 9-1, Tabular schedule of evaluations
- Section 16.1 Vascular ultrasound substudy

15.1.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol, Version 1.0. In the display of modifications, the "old text" refers to the protocol version preceding this amendment; deletions are ~~crossed out~~. Additions are underlined in the "new text" or "added text."

15.1.2.1 Title page

The title page was modified based on amendment change 1.

Old Text:

[…]

Sponsor's study medical expert:	PPD ~~Bayer Vital GmbH, 51368 Leverkusen, Germany~~ ~~Phone No.~~ PPD

New Text:

[…]

Sponsor's study medical expert:	PPD Bayer HealthCare Pharmaceuticals Inc. 100 Bayer Blvd, PO Box 915 Whippany, NJ 07981-0915; United States Phone No. PPD

15.1.2.2 Section 2. Synopsis, Study objective(s)

Section revised per amendment change 8.

Old Text:

[…]

Secondary efficacy objectives:

- to evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of index limb revascularization;

[…]

- to evaluate ~~the efficacy of~~ rivaroxaban in reducing the risk of venous thromboembolic (VTE) events;
- to evaluate ~~the efficacy of~~ rivaroxaban in reducing the risk of all-cause mortality.

New Text:

[...]

Secondary efficacy objectives:

- to evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of index limb revascularization (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 venous thromboembolic (VTE) events;
- to evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of all-cause mortality.

15.1.2.3 Section 2. Synopsis, Background treatment

Section revised per amendment change 17.

Old Text:

All study patients will receive treatment with open label ASA 100 mg orally once daily (od) during the entire course of the study; additional treatment with clopidogrel may be administered for a planned duration of 30 days ~~following~~ the qualifying revascularization procedure, at the discretion of the investigator. ~~This extended use will be limited to a labeled indication for a device (e.g., stent) and will not exceed 60 days.~~

New Text:

All study patients will receive treatment with open label ASA 100 mg orally once daily (od) during the entire course of the study; additional treatment with clopidogrel may be administered for a planned duration of up to 30 days after the qualifying revascularization procedure (or up to 60 days for a labeled indication [e.g. drug coated stent or balloon]), at the discretion of the investigator

15.1.2.4 Section 2. Synopsis, Diagnosis and main criteria for inclusion/exclusion

Section revised per amendment changes 4, 5, 7, 17 and 20.

Old Text:

Main inclusion criteria are:

- age ≥50,
- documented moderate to severe symptomatic lower extremity peripheral artery ~~occlusive~~ disease as evidenced by ALL of the following:
  a. clinically, by functional limitations in walking activity, ischemic rest pain, or ischemic ulceration,
  b. anatomically, by imaging evidence of ~~arterial occlusive~~ disease ~~below the inguinal ligament~~ within ~~6~~ months prior to or at the time of the qualifying revascularization,

AND

c. hemodynamically (within ~~6~~ months prior to, or at the time of, the qualifying revascularization) by:
   - an ABI ≤ 0.80 or TBI ≤ 0.60 ~~of the index leg (in the event of non-compressible ankle arteries)~~ for patients without a prior history of limb revascularization ~~on the index leg~~,

   OR

   - an ABI ≤ 0.85 or TBI ≤ 0.65 ~~of the index leg (in the event of non-compressible ankle arteries)~~ for patients with a prior history of limb revascularization ~~on the index leg~~.

Main exclusion criteria are:

- patients undergoing revascularization for asymptomatic PAD, mild claudication without functional limitation ~~or major tissue loss (including severe ischemic ulcers or gangrene) of the index leg~~,
- patients undergoing revascularization of the index leg to treat an asymptomatic or minimally symptomatic restenosis of a bypass graft or target lesion restenosis,
- prior revascularization on the index leg within ~~8 weeks~~ of the qualifying revascularization,
- Planned dual antiplatelet therapy (DAPT) use for the qualifying revascularization procedure of clopidogrel in addition to ASA for >30 days after the qualifying revascularization procedure
- Planned DAPT use for any other indication(s) with any P2Y12 antagonists in addition to ASA after the qualifying revascularization procedure

New Text:

Main inclusion criteria are:

- age ≥50,
- documented moderate to severe symptomatic lower extremity atherosclerotic peripheral artery disease as evidenced by ALL of the following:
  a. clinically, by functional limitations in walking activity, ischemic rest pain, or ischemic ulceration,
  b. anatomically, by imaging evidence of peripheral artery disease distal to the external iliac artery in the index leg within 12 months prior to or at the time of the qualifying revascularization,

  AND

  c. hemodynamically in either leg (within 12 months prior to, or at the time of, the qualifying revascularization) by:
     - an ABI ≤ 0.80 or TBI ≤ 0.60 for patients without a prior history of limb revascularization,

     OR

     - an ABI ≤ 0.85 or TBI ≤ 0.65 for patients with a prior history of limb revascularization.

Main exclusion criteria are:

- patients undergoing revascularization for asymptomatic PAD, or mild claudication

without functional limitation,
- patients undergoing revascularization of the index leg to treat an asymptomatic or minimally symptomatic restenosis of a bypass graft or target lesion restenosis,
- prior revascularization on the index leg within 10 days of the qualifying revascularization,
- Planned dual antiplatelet therapy (DAPT) use for the qualifying revascularization procedure of clopidogrel in addition to ASA for >30 days after the qualifying revascularization procedure (or > 60 days for a labeled indication [e.g. drug coated stent or ballon]) (**Planned use of clopidogrel not exceeding 60 days for a labeled indication for a device [e.g., stent or balloon] may be allowed; see section 8.1 for further guidance on clopidogrel*),
- Planned DAPT use for any other indication(s) with any P2Y12 antagonists in addition to ASA after the qualifying revascularization procedure

15.1.2.5 Section 2. Synopsis, Methodology

Section revised per amendment changes 2 and 3.

Old Text:

[...]

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), and treatments will be balanced within a country for each stratum by block randomization. Randomization and study treatment will commence as soon as possible but no later than ~~7~~ days after the qualifying revascularization.

The first study visit is a screening visit to be performed within ~~7~~ days after the qualifying revascularization. The second study visit is the randomization visit, which should be performed as soon as possible (but no later than ~~7~~ days) after the qualifying revascularization. The first dose of study drug ~~will~~ be taken at the randomization visit

New Text:

[...]

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), and treatments will be balanced within a country for each stratum by block randomization. Randomization and study treatment will commence as soon as possible but no later than 10 days after the qualifying revascularization.

The first study visit is a screening visit to be performed within 30 days prior to or no more than 10 days after the qualifying revascularization. The second study visit is the randomization visit, which should be performed as soon as possible (but no later than 10 days) after the qualifying revascularization. The first dose of study drug should be taken at the randomization visit

15.1.2.6 Section 2. Synopsis, Primary and secondary variable(s)

Section revised per amendment change 8.

Old Text:

[...]

The secondary efficacy variables of the study will be:

- time from randomization to the first occurrence of an index limb revascularization;

New Text:

[...]

The secondary efficacy variables of the study will be:

- time from randomization to the first occurrence of an index leg limb revascularization (subsequent to index procedure that was not planned or considered part of the initial treatment plan at the time of randomization);

15.1.2.7 Definition of medical terms

Section revised per amendment changes 4, 6 and 7.

Old Text:

[...]

Endovascular procedure	Refers to **c**atheter-based and hybrid procedures (those procedures involving aspects of both endovascular and surgical revascularizations).
Index leg	Refers to the leg receiving the qualifying revascularization for randomization into this trial. ~~In the event that revascularization is planned on both legs, the index leg will be defined as the most symptomatic one.~~
Qualifying revascularization	Refers to the procedure by which the patient qualifies for the study. ~~The qualifying revascularization procedure for patients that require multiple attempts at revascularization on the index leg and lesion must be the last of the planned/foreseeable revascularizations~~.

[...]

Surgical procedure	Refers to surgical bypass procedure in the lower extremity for PAD ~~below the inguinal ligament~~. This can include a variety of bypass conduit materials and extra-anatomic operations.

New Text:

[…]

Endovascular procedure	Refers to **c**atheter-based and hybrid procedures (those procedures involving aspects of both endovascular and surgical revascularizations) for PAD distal to the external iliac artery.
Index leg	Refers to the leg receiving the qualifying revascularization for randomization into this trial.
Qualifying revascularization	Refers to the procedure by which the patient qualifies for the study.

[…]

Surgical procedure	Refers to surgical bypass procedure in the lower extremity for PAD distal to the external iliac artery. This can include a variety of bypass conduit materials and extra-anatomic operations.

15.1.2.8 Section 3.4. Benefit/risk assessment

Section revised per amendment change 16.

Old Text:

[…]

The safety profile of rivaroxaban is based on an extensive database of safety information collected in a substantial clinical development program, which has enrolled over 84,000 patients into phase 2 and 3 clinical trials alone, including over 47,000 patients treated with rivaroxaban. In addition, the steadily amassing post-marketing data summarized in numerous Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Reports (PBRERs), corresponding to an estimated cumulative patient exposure of 3.7 million patient years, provides further reassurance about rivaroxaban benefit-risk balance in the real-life setting. In conclusion, no undue safety risks are expected from the interventional drug treatment with rivaroxaban in the present study.

New Text:

[…]

The safety profile of rivaroxaban is based on an extensive database of safety information collected in a substantial clinical development program, which has enrolled as of Sep 2015 more than 108,000 subjects have been enrolled in interventional clinical trials (completed and ongoing Phase I, Phase II, Phase III and Phase IV) including more than 60,000 subjects treated with rivaroxaban. In addition, the steadily amassing post-marketing data summarized in numerous Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Reports (PBRERs), corresponding to an estimated cumulative patient exposure of 3.7 million patient years, provides further reassurance about rivaroxaban benefit-risk balance in the real-life setting. In conclusion, no undue safety risks are expected from the interventional drug

treatment with rivaroxaban in the present study. Further details can be found in the latest available version of the investigator's brochure, which contains comprehensive information on the study drug.[106]

15.1.2.9 Section 4. Study objectives

Section revised per amendment change 8.

Old Text:

[...]

The secondary efficacy objectives of the study are:

- to evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of index limb revascularization;

[...]

- to evaluate ~~the efficacy of~~ rivaroxaban in reducing the risk of venous thromboembolic (VTE) events;
- to evaluate ~~the efficacy of~~ rivaroxaban in reducing the risk of all-cause mortality.

New Text:

[...]

The secondary efficacy objectives of the study are:

- to evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of index limb revascularization (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 venous thromboembolic (VTE) events;
- to evaluate whether rivaroxaban added to ASA is superior to ASA alone in reducing the risk of all-cause mortality.

15.1.2.10 Section 5. Study design

Section revised per amendment changes 2, 3 and 17.

Old Text:

[...]

….Randomization and study treatment should commence as soon as possible but no later than ~~7~~ days after a successful qualifying revascularization procedure and once hemostasis has been assured. All randomized patients 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.

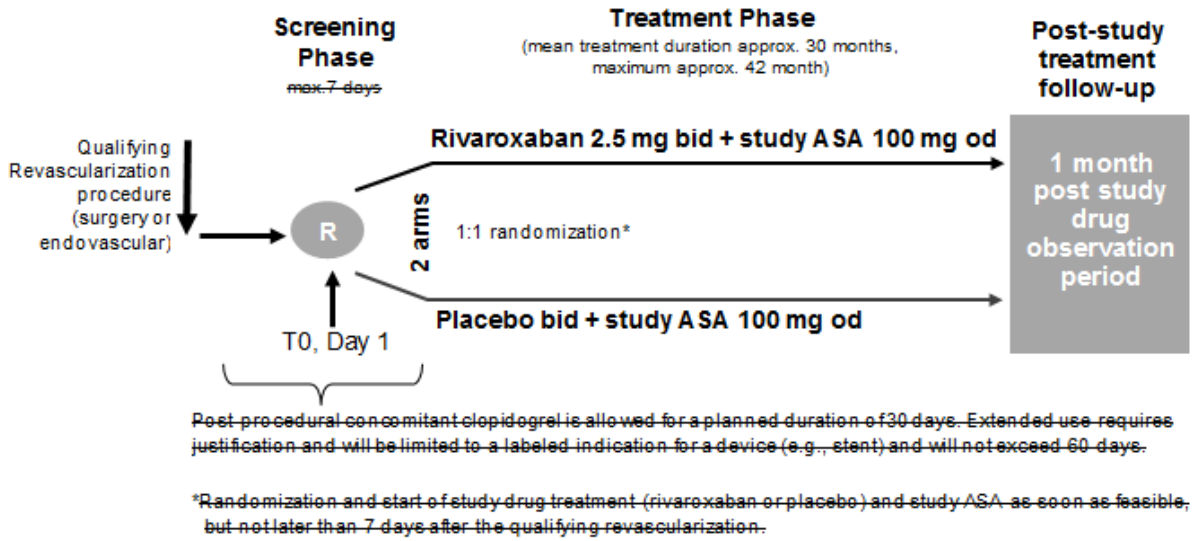
---

106 Sentence was added with Protocol Amendment 4 (change no. 16).

The first study visit is a screening visit to be performed within ~~7~~ days after the qualifying revascularization. The second study visit is the randomization visit (randomization will be assigned as T0 on the time axis). The first study drug dose ~~will~~ be ~~taken at~~ the randomization visit. The screening and randomization visits can be combined into one visit if all tests required for the assessment of all eligibility criteria are available and randomization and dosing can be performed on a single day.

[...]

Figure 5-1: Study design



New Text:

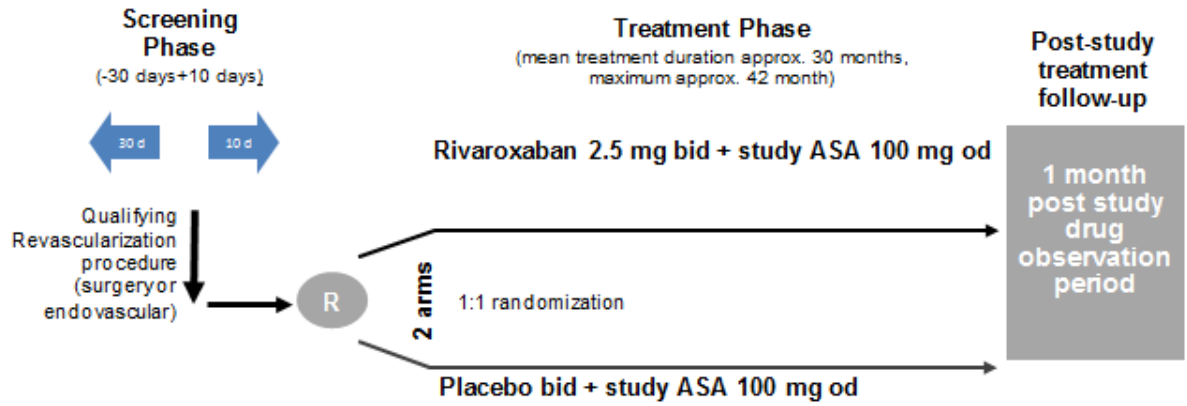
[...]

….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 patients 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 first study visit is a screening visit to be performed within 30 days prior to or no more than 10 days after the qualifying revascularization. The second study visit is the randomization visit (randomization will be assigned as T0 on the time axis). The first study drug dose should be administered as close to the time of the randomization visit as possible (See Section 7.4 for additional guidance on dosing at randomization). The screening and randomization visits can be combined into one visit if all tests required for the assessment of all eligibility criteria are available and randomization and dosing can be performed on a single day.

[...]

Figure 5-1: Study design



15.1.2.11 Section 6.1. Inclusion criteria

Section revised per amendment changes 2, 4, 5, and 20a-c.

Old Text:

[...]

2. Documented moderate to severe symptomatic lower extremity peripheral artery ~~occlusive~~ disease as evidenced by ALL of the following:

   a. clinically, by functional limitations in walking activity, ischemic rest pain, or ischemic ulceration,

   b. anatomically, by imaging evidence of ~~occlusive PAD~~ ~~below the inguinal ligament~~ within ~~6~~ months prior to or at the time of the qualifying revascularization,

   AND

   c. hemodynamically (within ~~6~~ months prior to, or at the time of, the qualifying revascularization) by:

      - an ABI ≤ 0.80 or TBI ≤ 0.60 ~~of the index leg (in the event of non-compressible ankle arteries)~~ for patients without a prior history of limb revascularization ~~on the index leg~~,

        OR

      - an ABI ≤ 0.85 or TBI ≤ 0.65 ~~of the index leg (in the event of non-compressible ankle arteries)~~ for patients with a prior history of limb revascularization ~~on the index leg~~.

3. Technically successful peripheral ~~infra-inguinal~~ revascularization (surgical and/or endovascular; for definition see Section 9.3.3) for symptomatic PAD within the last ~~7~~ days prior to randomization;

[...]

7. Women ~~and men~~ of reproductive potential must agree to use adequate contraception* when sexually active. This applies for the time period between signing of the informed consent form (ICF) ~~and after~~ the last administration of study drug.

*(*The definition of adequate contraception will be based on the judgment of the investigator and on local requirements. Acceptable methods of contraception include, but are not limited to, ~~(i) condoms (male or female) with or without a spermicidal agent; (ii) diaphragm or cervical cap with spermicide; (iii) intra-uterine device; (iv) hormone-based contraception. Patients must agree to utilize two reliable and acceptable methods of contraception simultaneously).~~*

[…]

New Text:

[…]

2. Documented moderate to severe symptomatic lower extremity atherosclerotic peripheral artery disease as evidenced by ALL of the following:
   a. clinically, by functional limitations in walking activity, ischemic rest pain, or ischemic ulceration,
   b. anatomically, by imaging evidence of peripheral artery disease distal to the external iliac artery in the index leg within 12 months prior to or at the time of the qualifying revascularization,

   AND

   c. hemodynamically in either leg (within 12 months prior to, or at the time of, the qualifying revascularization) by:
      - an ABI ≤ 0.80 or TBI ≤ 0.60 for patients without a prior history of limb revascularization,

      OR

      - an ABI ≤ 0.85 or TBI ≤ 0.65 for patients with a prior history of limb revascularization.
3. Technically successful peripheral revascularization distal to the external iliac artery (surgical and/or endovascular; for definition see Section 9.3.3) for symptomatic PAD within the last 10 days prior to randomization;

[…]

7. Women of reproductive potential must agree to use adequate contraception* when sexually active. This applies for the time period between signing of the informed consent form (ICF) to the last administration of study drug.
   *(*The definition of adequate contraception [with a failure rate of less than 1% per year] will be based on the judgment of the investigator and on local requirements. Acceptable methods of contraception include, but are not limited to: oral contraceptives, contraceptive injections, intrauterine device, double barrier method, male partner sterilization).*

[…]

15.1.2.12 Section 6.2 Exclusion criteria

Section revised per amendment changes 7, 15, 17 and 18.

Old Text:

1. Patients undergoing revascularization for asymptomatic PAD~~,~~ mild claudication without functional limitation ~~or major tissue loss (including severe ischemic ulcers or gangrene)~~ of the index leg;

[...]

3. Prior revascularization on the index leg within ~~8 weeks~~ of the qualifying revascularization;

[...]

- Exclusion criteria related to concomitant and study treatment:

5. Patients requiring treatment with ASA at doses >100 mg;
6. Planned dual antiplatelet therapy (DAPT) use for the qualifying revascularization procedure of clopidogrel in addition to ASA for >30 days* after the qualifying revascularization procedure
   **Use of clopidogrel not exceeding 60 days for a labeled indication for a device [e.g., stent or balloon] may be allowed ~~with written justification of the investigator~~*)

[...]

12. Medical history or active clinically significant bleeding, lesions, or conditions within the last 6 months prior to randomization, considered to be a significant risk for major bleeding (this may include current medically confirmed gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, current or recent brain or spinal injury, known esophageal varices, vascular aneurysms of the large arteries or major intraspinal or intracerebral vascular abnormalities; ~~patients without any medical history of gastrointestinal disease may be exempted from this exclusion criterion~~);

[...]

23. Previous (within 30 days) or concomitant participation in another clinical study with investigational ~~medicinal~~ product

24. Close affiliation with the investigational site; e.g., a close relative of the investigator, dependent person (e.g., employee or student of the investigational site).

New Text:

1. Patients undergoing revascularization for asymptomatic PAD <u>or</u> mild claudication without functional limitation of the index leg;

[...]

3. Prior revascularization on the index leg within <u>10 days</u> of the qualifying revascularization;

[...]

5. <u>Patients with major tissue loss (defined as significant ulceration/gangrene proximal to the metatarsal heads, i.e. heel or midfoot) in either leg.</u>

- Exclusion criteria related to concomitant and study treatment:

6. Patients requiring treatment with ASA at doses >100 mg;
7. Planned dual antiplatelet therapy (DAPT) use for the qualifying revascularization procedure of clopidogrel in addition to ASA for >30 days* after the qualifying revascularization procedure (or > 60 days for a labeled indication [e.g. drug coated stent or balloon])
   **Planned use of clopidogrel not exceeding 60 days for a labeled indication for a device [e.g., stent or balloon] may be allowed; see section 8.1 for further guidance on clopidogrel)*

[...]

12. Medical history or active clinically significant bleeding, lesions, or conditions within the last 6 months prior to randomization, considered to be a significant risk for major bleeding (this may include current medically confirmed gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, current or recent brain or spinal injury, known esophageal varices, vascular aneurysms of the large arteries or major intraspinal or intracerebral vascular abnormalities);

[...]

23. Previous (within 30 days) or concomitant participation in another clinical study with investigational product
24. Close affiliation with the investigational site; e.g., a close relative of the investigator, dependent person (e.g., employee or student of the investigational site).
25. Breast feeding

15.1.2.13 Section 6.3.1 Discontinuation and withdrawal

Section revised per amendment change 16.

Old Text:

[...]

- pregnancy
- if, in the investigator's opinion, continuation of the study drug would be harmful to the patient's well-being (e.g. significant decline in cognitive function or renal failure with eGFR <15 mL/min/1.73 m^2),
- at the specific request of the sponsor and in liaison with the investigator (e.g., safety concerns).

[...]

New Text:

[...]

- pregnancy

Patients may be withdrawn from study drug, if any of the following occurs:

- if, in the investigator's opinion, continuation of the study drug would be harmful to the patient's well-being (e.g. significant decline in cognitive function or renal failure with eGFR <15 mL/min/1.73 m^2),
- at the specific request of the sponsor and in liaison with the investigator (e.g., safety concerns).

15.1.2.14 Section 7.1. Treatments to be administered

Section revised per amendment change 17.

Old Text:

[...]

In either treatment group, post-procedural concomitant treatment with clopidogrel will be allowed ~~for a planned maximum period of 30 days following the qualifying revascularization procedure. Justification will need to be provided if the investigator would like to treat the patient with clopidogrel for longer than 30 days following the revascularization. This extended use will be limited to a labeled indication for the device (e.g., stent) and will not exceed 60 days. Clopidogrel will not be part of or provided as study medication.~~

New Text:

[...]

In either treatment group, post-procedural concomitant treatment with clopidogrel will be allowed as described in Section 8.1.

15.1.2.15 Section 7.4. Dosage and administration

Section revised per amendment change 17.

Old Text:

[...]

Clopidogrel (at a dose that is consistent with the site/country's standard of care) may be used ~~for DAPT in either treatment group for a planned period of up to 30 days (or up to 60 days, if justified; see Section 7.1) after the qualifying revascularization procedure~~ at the discretion of the investigator.

New Text:

[...]

Clopidogrel (at a dose that is consistent with the site/country's standard of care) may be used at the discretion of the investigator as described in Section 8.1.

15.1.2.16 Section 7.4.1 Dosage modifications

Section revised per amendment change 16.

Old Text:

[...]

The following sections provide general guidance for use of rivaroxaban. ~~For further details, please refer to the investigator brochure (IB) and/or applicable local product information~~. For use of ASA, please refer to applicable guidelines and local production information.

New Text:

[...]

The following sections provide general guidance for use of rivaroxaban. For use of ASA, please refer to applicable guidelines and local production information.

15.1.2.17 Section 7.4.4. Guidance for the treatment of subjects who develop an acute coronary syndrome and those who require percutaneous coronary intervention with stenting

Section revised per amendment change 17.

Old Text:

Study medication should be temporarily interrupted in patients who require anticoagulant or DAPT because of an ACS or ~~need~~ for percutaneous coronary intervention (PCI) with stenting. Peri-procedurally, standard antiplatelet therapy, including ASA and clopidogrel (or other P2Y12 antagonists such as prasugrel or ticagrelor) can be administered according to usual practice. Study ASA may be continued. Standard anticoagulant therapy can be ~~used~~ without regard to the timing of the most recent dose of study medication because the dose of rivaroxaban being tested in this trial is significantly lower than the 15 or 20 mg dose administered for stroke prevention in ~~atrial~~ non-valvular fibrillation and the half-life of rivaroxaban is short, only 5-13 hours.

Following the procedure, decision and timing to resume study medication are at the discretion of the treating physician and the investigator. If medically indicated, study medication may be used along with DAPT or interrupted until patient no longer requires DAPT.

New Text:

Study medication should be temporarily interrupted in patients who require anticoagulant or DAPT because of an ACS <u>event</u> or for percutaneous coronary intervention (PCI) with stenting. Peri-procedurally, standard antiplatelet therapy, including ASA and clopidogrel (or other P2Y12 antagonists such as prasugrel or ticagrelor) can be administered according to usual practice. Study ASA may be continued. Standard anticoagulant therapy can be <u>initiated</u> without regard to the timing of the most recent dose of study medication because the dose of rivaroxaban being tested in this trial is significantly lower than the 15 or 20 mg dose administered for stroke prevention in non-valvular atrial fibrillation and the half-life of rivaroxaban is short, only 5-13 hours.

Following the procedure, the decision and timing to resume study medication are at the discretion of the treating physician and the investigator. If medically indicated, study

medication may be used along with DAPT with clopidogrel as described in Section 8.1, or interrupted until patient no longer requires DAPT.

15.1.2.18 Section 8.1. Prior and concomitant therapy

Section revised per amendment changes 9, 17 and 22 a-d.

Old Text:

Generally, all prior (within 30 days prior to ~~screening~~) and concomitantly taken drugs (as specified in the eCRF) need to be recorded in the eCRF.

[…]

In addition, any remedial therapy for non-serious-AEs (if AEs are subject to ~~documentation~~) should be documented.

Clopidogrel and other non-study antiplatelet treatment

Patients who enter the study receiving additional antiplatelet therapy will have non-study antiplatelet therapy discontinued when study medication is started. ~~The use of clopidogrel for a planned duration of 30 days following the qualifying revascularization procedure is allowed if deemed required by the investigator, but will not be supplied as a study medication. Justification will need to be provided if the investigator would like to treat the patient with clopidogrel for longer than 30 days following the revascularization. This extended use will be limited to a labeled indication for the device (e.g., stent) and will not exceed 60 days.~~

~~Patients who require use of clopidogrel during the course of the study after the qualifying revascularization procedure (e.g., indication for PCI with or without stenting), use of clopidogrel or DAPT is allowed (see Section 7.4.4). If medically indicated, study medication may be used along with DAPT or interrupted until the patient no longer requires DAPT.~~

[…]

Prohibited therapy while on study medication

[…]

- use of antiplatelet therapy other than the protocol specified background antiplatelet therapy of study ASA or clopidogrel is prohibited during the study. This includes drugs with known significant antiplatelet effects such as cilostazol;
- additional anticoagulant(s) (e.g., warfarin sodium or vitamin K antagonists, Factor II or Xa inhibitors) concomitantly with study medication are prohibited. ~~Study medication shall be discontinued in patients who develop any condition which requires permanent or long term anticoagulation (e.g., DVT, atrial fibrillation~~.

[…]

These prohibited therapies may be administered on a temporary basis, ~~and if administered~~ the investigator should consider temporarily discontinuing study medication if the treatment could result in an increased risk of bleeding (e.g., strong inhibitors of both CYP3A4 and P-gp, or anticoagulants).

[…]

Discontinuation of Study Drug for a Vascular Procedure

[...]

~~After PCI or CABG, treatment with DAPT should be considered for at least 48 hours.~~
Depending on the bleeding risk, the patient may, at the discretion of the managing physician, resume study medication thereafter, but no earlier than approximately 12 hours after the arterial sheath has been removed (for patients undergoing PCI) or after the post-procedural drains have been removed (for patients undergoing CABG surgery), and the last dose of parenteral anticoagulant therapy has been administered.

[...]

New Text:

Generally, all prior (within 30 days prior to randomization) and concomitantly taken drugs (as specified in the eCRF) need to be recorded in the eCRF

[...]

In addition, any remedial therapy for non-serious-AEs (if AEs are subject to reporting) should be documented.

Clopidogrel and other non-study antiplatelet treatment

Patients who enter the study receiving additional antiplatelet therapy will have non-study antiplatelet therapy discontinued when study medication is started.

If deemed required by the investigator, the use of clopidogrel for a planned duration of up to 30 days following the qualifying revascularization procedure, or planned duration of up to 60 days in the case of a labeled indication for a device (e.g. drug-coated stent or balloon), is allowed. Justification will need to be documented during the course of this planned use of clopidogrel if the investigator determines that a medical need arises that warrants that clopidogrel be administered for >30 days following the qualifying revascularization, or >60 days in the case of a device. Clopidogrel will not be supplied as a study medication.

During the course of the study, for enrolled patients who require use of clopidogrel for a new indication (e.g., indication for PCI with or without stenting), use of clopidogrel is allowed (see Section 7.4.4). At the discretion of the investigator, study medication may be used along with clopidogrel or interrupted until the patient no longer requires clopidogrel. The duration of clopidogrel use should follow standard of care and applicable international guidelines.

Treatment with other P2Y12 antagonists, such as prasugrel or ticagrelor may be administered according to usual practice, but the study drug must be interrupted if such drugs are used long-term.

[...]

Prohibited therapy while on study medication

[...]

- use of antiplatelet therapy other than the protocol specified background antiplatelet therapy of study ASA or clopidogrel is prohibited during the study. This includes drugs with known significant antiplatelet effects such as cilostazol, prasugrel, and ticagrelor;

- additional anticoagulant(s) (e.g., warfarin sodium or vitamin K antagonists, heparins, Factor II or Xa inhibitors) concomitantly with study medication are prohibited.

[...]

These prohibited therapies may be administered on a temporary basis in combination with the study drug if deemed medically appropriate. In general, the investigator should consider temporarily discontinuing study medication if the treatment could result in an increased risk of bleeding (e.g., strong inhibitors of both CYP3A4 and P-gp, or anticoagulants).

[...]

Discontinuation of Study Drug for a Vascular Procedure

[...]

Depending on the bleeding risk, the patient may, at the discretion of the managing physician, resume study medication thereafter, but no earlier than approximately 12 hours after the arterial sheath has been removed (for patients undergoing PCI) or after the post-procedural drains have been removed (for patients undergoing CABG surgery), and the last dose of parenteral anticoagulant therapy has been administered.

[...]

15.1.2.19 Section 9.1. Tabular schedule of evaluations

Section revised per amendment changes 2, 3,5, 6, 10, 12, and 17.

Old Text:

[...]

Patients will be assessed for study participation after the qualifying revascularization whereas this procedure is not considered to be a study visit. On-site study visits for the patients at the investigational site are planned at Screening, Randomization, 1, 3, 6, and 12 months after randomization, and then every 6 months until the end of the study. Upon announcement of study end, patients will come to the clinic for a final on-site EOT visit followed by a telephone contact (post-study treatment follow-up visit) one month later.

The following visit abbreviations are used in the description of the visit schedule:

Rev: Day of the qualifying revascularization procedure (not considered a study visit).

ScV: Screening visit (to be performed ~~within 7 days~~ after Rev; screening procedures can be performed over multiple days if necessary).

RxV: Randomization visit (time point of randomization = [T0]), to be performed as soon as possible but no later than ~~7~~ days after Rev once hemostasis is assured.

[...]

Clinic visits should be scheduled as close to the specified interval as possible, and preferably within the defined window. If it is not possible for the patient to return within the visit "window", especially due to unforeseen circumstance beyond the control of the patient or the study center, then the visit should be scheduled as close to the interval as is convenient for the patient and the study center.

~~At selected qualified sites, a duplex ultrasound evaluated of the treated leg may be performed to measure lumen diameter and vessel patency in order to understand mechanistic effects of study treatment (see Appendix 16.1).~~

Table 9-1: Schedule of assessments

Timelines	Qualifying revascular-ization (Rev)	ScV [a]	RxV [a] (T0)	Treatment Phase V1 1 Mo	V2 3 Mo	V3 6 Mo	V4 12 Mo	V5-Vx every 6 Mo	EOT visit [b]	PS-FU 1 Mo post EOT
Visit Window (weeks if not otherwise specified)		**Up to +7 days after Rev**	**Up to +7 days after Rev**	**±10 days**	**±4**	**±4**	**±4**	**±4**		**±1**
Type of Visit		**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	☎
Informed consent		●								
Demographics		●								
Medical / surgical history		●								
Laboratory tests [c]		●								
Serum pregnancy test [d]		●								
Inclusion/Exclusion		●								
Revascularization procedure (surgical or endovascular)	♦									
Documentation of revascularization details		●								
Randomization (IxRS)			●							
Concomitant medications [e]		●	●	●	●	●	●	●	●	
1st study drug			●							
Drug dispense			●	●	●	●	●	●		
Drug accountability				●	●	●	●	●	●	
Vital Signs		●	●	●	●	●	●	●	●	
Study efficacy outcomes		●	←	continuous reporting						→
Study safety outcomes (bleeding events)		●	←	continuous reporting						→
AE/SAE reporting [f]		●	●	●	●	●	●	●	●	●
ABI/TBI		● [g]	●	●	●	●	●	●	●	
Questionnaires (EQ-5D, WIQ, PRO)		● [h]		●	●	●	●	●	●	
Vital status										●
Duplex Ultrasound [j]				●		●				

(footnotes are provided on the next page)

♦ = procedure ~~before study (not study-related)~~; ● = study procedure to be performed at specified visits; ☎ = post-study treatment telephone contact
Abbreviations: ABI/TBI = Ankle (Toe) - Brachial - Index; AE = adverse event; EOT = end of treatment; EQ-5D = European Quality of Life-5 Dimensions questionnaire; IxRS = Interactive Voice and Web Response System; Mo = month; V = visit; Rx = randomization; SAE = serious adverse event; Sc = Screening; WIQ = Walking Impairment Questionnaire, ~~PRO = patient-reported outcomes data~~

a: Screening visit can be performed at the same time as randomization visit, if all required tests for eligibility criteria are available at that time. ~~Maximum screening~~ period is ~~7~~ days after the revascularization procedure. Randomization should be done as soon as possible (but within ~~7~~ days) after the qualifying revascularization procedure.

b: End of treatment visit is to be performed within 4 weeks after announcement of study end, or once the patient has permanently withdrawn from the study.

c: Laboratory tests required to verify the eligibility criteria (creatinine/eGFR~~, serum pregnancy test~~) are to be collected per the site's standard of care and assessed through a local lab ~~and~~ must not be older than ~~7~~ days prior to ~~randomization~~. If the patient's eGFR is <30 mL/min/1.73 m^2 prior to the procedure, it must remain to be >15 mL/min/1.73 m^2 72 hours after the procedure to enroll and randomize the patient.

d: Required in women of childbearing potential only.

e: Planned post-procedural concomitant clopidogrel allowed ~~for a maximum period~~ of ~~30 days (an extended use of up to 60 days will be accepted in a labeled indication~~; see Section ~~7.1~~).

f: Only AE/ SAEs not exempted from adverse event reporting and specified in the need to be documented (see Section 9.6.1.2.6).

g: ABI/TBI values used at screening may be historical (captured in the patient's medical history), but must not be older than ~~6~~ months prior to the qualifying revascularization procedure.

h: ~~Baseline assessments~~ can be performed ~~either at the~~ screening ~~visit or the randomization visit~~.

j: ~~Duplex ultrasound of the treated limb(s) (at selected sites only).~~

New Text:

[...]

Patients will be assessed for study participation prior to, or after, the qualifying revascularization whereas this procedure is not considered to be a study visit. On-site study visits for the patients at the investigational site are planned at Screening, Randomization, 1, 3, 6, and 12 months after randomization, and then every 6 months until the end of the study. Upon announcement of study end, patients will come to the clinic for a final on-site EOT visit followed by a telephone contact (post-study treatment follow-up visit) one month later.

The following visit abbreviations are used in the description of the visit schedule:

ScV: Screening visit (to be performed up to 30 days prior to but no later than 10 days after Rev; screening procedures can be performed over multiple days if necessary).

Rev: Day of the qualifying revascularization procedure (not considered a study visit).

RxV: Randomization visit (time point of randomization = [T0]), to be performed as soon as possible but no later than 10 days after Rev once hemostasis is assured.

[...]

Clinic visits or procedures should be scheduled as close to the specified interval as possible, and preferably within the defined window. If it is not possible for the patient to return within the visit "window," or perform the required study procedures, especially due to unforeseen circumstance or technical feasibility beyond the control of the patient or the study center, then the visit or procedure should be scheduled as close to the interval as is convenient for the patient and the study center.

The new schedule of assessment includes the changes according to amendment 4. The respective footnotes, however, were not repeated in the new text version for better readability. Please refer to the revised schedule of assessment in Section 9.1

Table 9-1: Schedule of assessments - amended

Timelines	ScV [a]	Qualifying revascular-ization (Rev)	RxV [a] (T0)	Treatment Phase V1 1 Mo	V2 3 Mo	V3 6 Mo	V4 12 Mo	V5-Vx every 6 Mo	EOT visit [b]	PS-FU 1 Mo post EOT
Visit Window (weeks if not otherwise specified)	**-30 days before, to +10 days after, Rev**		**Up to +10 days after Rev**	**±10 days**	**±4**	**±4**	**±4**	**±4**		**±1**
Type of Visit	**Visit**		**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	☎
Informed consent	●									
Demographics	●									
Medical / surgical history	●									
Laboratory tests [c]	●									
Serum pregnancy test [d]	●									
Inclusion/Exclusion	●									
Revascularization procedure (surgical or endovascular)		♦								
Documentation of revascularization details			●[46]							
Randomization (IxRS)			●							
Concomitant medications [e]	●		●	●	●	●	●	●	●	
1st study drug			●							
Drug dispense			●	●	●	●	●	●		
Drug accountability				●	●	●	●	●	●	
Vital Signs	●		●	●	●	●	●	●	●	
Study efficacy outcomes	● ←			continuous reporting						→
Study safety outcomes (bleeding events)	● ←			continuous reporting						→
AE/SAE reporting [f]	●		●	●	●	●	●	●	●	●
ABI/TBI	● [g]			●	●	●	●	●	●	
Questionnaires (EQ-5D, WIQ, HCRU) PAD symptom status			●	●	●	●	●	●	●	
Vital status										●

Table 9-1: Schedule of assessments - amended

Timelines	ScV [a]	Qualifying revascular-ization (Rev)	RxV [a] (T0)	Treatment Phase						PS-FU 1 Mo post EOT
				V1	V2	V3	V4	V5-Vx	EOT visit [b]	
				1 Mo	3 Mo	6 Mo	12 Mo	every 6 Mo		
Visit Window (weeks if not otherwise specified)	**-30 days before, to +10 days after, Rev**		**Up to +10 days after Rev**	**±10 days**	**±4**	**±4**	**±4**	**±4**		**±1**

♦ = non-study procedure (*change no. 17*); ● = study procedure to be performed at specified visits; ☎ = post-study treatment telephone contact

Abbreviations: ABI/TBI = Ankle (Toe) - Brachial - Index; AE = adverse event; EOT = end of treatment; EQ-5D = European Quality of Life-5 Dimensions questionnaire; IxRS = Interactive Voice and Web Response System; Mo = month; V = visit; Rx = randomization; SAE = serious adverse event; Sc = Screening; WIQ = Walking Impairment Questionnaire, HCRU=Health Care Research Utilization data (see Section 9.7.3) (*change 17*)

a: Screening visit can be performed at the same time as randomization visit, if all required tests for eligibility criteria are available at that time. Screening period is 30 days before or up to 10 days (*change no. 3)* after the revascularization procedure. Randomization should be done as soon as possible (but within 10 days [*change no. 2*]) after the qualifying revascularization procedure.

b: End of treatment visit is to be performed within 4 weeks after announcement of study end, or once the patient has permanently withdrawn from the study.

c: Laboratory tests required to verify the eligibility criteria (creatinine/eGFR) are to be collected per the site's standard of care and assessed through a local lab. Creatinine/eGFR must not be older than 30 days prior to the qualifying revascularization (*change no. 10*). If the patient's eGFR is <30 mL/min/1.73 m^2 prior to the procedure, it must remain to be >15 mL/min/1.73 m^2 72 hours after the procedure in order (*change no. 17*) to enroll and randomize the patient.

d: Required in women of childbearing potential only. A pregnancy test must not be older than 7 days prior to randomization.

e: Planned post-procedural concomitant clopidogrel allowed at the discretion of the investigator, see Section 8.1

f: Only AE/ SAEs not exempted from adverse event reporting and specified in the need to be documented (see Section 9.6.1.3) (change no 17).

g: ABI/TBI values used at screening may be historical (captured in the patient's medical history), but must not be older than 12 months prior to the qualifying revascularization procedure (*change no. 5*). If an ABI/TBI is performed during screening to assess eligibility, it must be completed prior to the qualifying revascularization (*change no. 6*).

15.1.2.20 Section 9.2.1.1. Screening Visit (ScV)

Section revised per amendment changes 3, 5, 10 and 17.

Old Text:

9.2.1.1 Screening Visit (ScV): after qualifying revascularization procedure ~~(study Day –7 to study Day 0)~~

~~Once a patient has received a lower limb revascularization procedure that qualify him/her for the study, he/she should be screened for eligibility for study participation.~~ The ScV is required to assess the eligibility of the patient. After obtaining signed informed consent, the investigator will review or perform all medical evaluations required to verify the patient's eligibility for study participation as defined in the inclusion and exclusion criteria. Adverse events reporting begins once the informed consent has been signed.

Demographic data and medical history (including PAD risk factors and vascular disease history) will be recorded at Screening. Laboratory tests should be performed according to the site specific standards, but must, at minimum, include creatinine and eGFR, and a serum pregnancy test in women of childbearing potential. Results of laboratory measurements (ideally obtained during the hospital admission for the qualifying revascularization) should not be older than ~~7~~ days prior to the qualifying revascularization; otherwise, tests would need to be repeated. If the site's local laboratory report does not provide eGFR, this value should be calculated (e.g. using the Modification of Diet in Renal Disease [MDRD] formula). All laboratory tests will be performed locally as no central laboratory is involved in this study.

The following measures/documentations will be performed at the screening visit:

- obtaining informed consent;
- documentation of demographic characteristics (for details see Section 9.3.1);
- ~~documentation of the details about the qualifying revascularization and its success;~~
- documentation of medical history (for details see Section 9.3.2) and surgical history;
- review laboratory test data for the patient, if creatinine/eGFR assessments were performed more than ~~7~~ days prior to the qualifying revascularization, they must be redrawn;
- ~~serum pregnancy test (in females with childbearing potential only);~~
- evaluate for all inclusion- and exclusion criteria;
- documentation of prior (within the last 30 days prior to ~~screening~~) and concomitant medication. Chronic treatment with prescription antiplatelet therapies (except already ongoing treatment with low-dose ASA that can be continued as study ASA 100 mg od) should be stopped;
- assess vital signs (blood pressure, pulse rate);
- check for the occurrence of AEs/SAEs since the signing of the ICF (only AEs/SAEs not exempted from AE/SAE reporting need to be reported; for details see Section ~~9.6.1.2.6~~);
- perform ABI (or TBI ~~for non-compressible tibial arteries~~) if no ABI/TBI data ~~is~~ available for the patient within the last ~~6~~ months prior to ~~screening~~;

- ~~QoL assessment with EQ-5D (this assessment can be performed at either the screening visit or the randomization visit);~~
- ~~Walking Impairment Questionnaire (this assessment can be performed at either the screening visit or the randomization visit).~~

If the patient is eligible for study participation, the site investigator should make all organizational arrangements required for prompt randomization of the patient to study treatment as soon as feasible, but no more than ~~7~~ days after the qualifying revascularization procedure (for treatments to be administered, see Section 7.1).

New Text:

9.2.1.1 Screening Visit (ScV): 30 days before, or up to 10 days after qualifying revascularization procedure

The ScV is required to assess the eligibility of the patient. After obtaining signed informed consent, the investigator will review or perform all medical evaluations required to verify the patient's eligibility for study participation as defined in the inclusion and exclusion criteria. Adverse events reporting begins once the informed consent has been signed.

Demographic data and medical history (including PAD risk factors and vascular disease history) will be recorded at Screening. Laboratory tests should be performed according to the site specific standards, but must, at minimum, include creatinine and eGFR, and a serum pregnancy test in women of childbearing potential. Results of laboratory measurements (ideally obtained during the hospital admission for the qualifying revascularization) should not be older than 30 days prior to the qualifying revascularization; otherwise, tests would need to be repeated. If the site's local laboratory report does not provide eGFR, this value should be calculated (e.g. using the Modification of Diet in Renal Disease [MDRD] formula). All laboratory tests will be performed locally as no central laboratory is involved in this study.

The following measures/documentations will be performed at the screening visit:

- obtaining informed consent;
- documentation of demographic characteristics (for details see Section 9.3.1);
- documentation of medical history (for details see Section 9.3.2) and surgical history;
- review laboratory test data for the patient, if creatinine/eGFR assessments were performed more than 30 days prior to the qualifying revascularization, they must be redrawn and if serum pregnancy test (females with childbearing potential only) was performed more than 7 days ago prior to the qualifying revascularization a repeat pregnancy test must be performed;
- evaluate for all inclusion- and exclusion criteria;
- documentation of prior (within the last 30 days prior to randomization) and concomitant medication. Chronic treatment with prescription antiplatelet therapies (except already ongoing treatment with low-dose ASA that can be continued as study ASA 100 mg od) should be stopped at the time of randomization;
- assess vital signs (blood pressure, pulse rate);

- check for the occurrence of AEs/SAEs since the signing of the ICF (only AEs/SAEs not exempted from AE/SAE reporting need to be reported; for details see Section 9.6.1.3);
- perform ABI (or TBI) if no ABI/TBI data are available for the patient within the last 12 months prior to the qualifying revascularization.

If the patient is eligible for study participation, the site investigator should make all organizational arrangements required for prompt randomization of the patient to study treatment as soon as feasible, but no more than 10 days after the qualifying revascularization procedure (for treatments to be administered, see Section 7.1).

15.1.2.21 Section 9.2.1.2. Randomization visit (RxV) 0-10 days after the qualifying revascularization procedure - amended

Section revised per amendment changes 2,12, 17 and 19.

Old Text:

9.2.1.2 Randomization visit (RxV): 0-~~7~~ days after the qualifying revascularization procedure

After meeting all inclusion criteria and none of the exclusion criteria, eligible patients will be randomized by accessing the IxRS system and receive study medication and study ASA as soon as feasible, but no more than ~~7~~ days after the qualifying revascularization procedure. The first dose of study medication ~~will~~ be given immediately after randomization. Planned additional treatment with clopidogrel ~~for up to 30 days (or up to 60 days, if justified by a labeled indication; see Section 7.1)~~ after the qualifying revascularization procedure is allowed at the discretion of the investigator.

The following measures/documentations will be performed at the randomization visit (~~study visit procedures should be performed in the order in which they are listed~~):

- randomization of patient;
- dispensing of study medication and study ASA with patient instruction;
- administration of first study medication treatment dose (on-site);
- documentation of any changes in concomitant medication since the last study visit;
- assess vital signs (blood pressure, pulse rate);
- check for the occurrence of study efficacy outcome events since the last study visit (these pre-randomization events should be documented on the outcome pages and forwarded by expedited means to the Sponsor's PV; see Section 9.6.1.2.6);
- check for the occurrence of study safety outcome events (bleeding events) since the last study visit (these pre-randomization events should be documented on the outcome pages and forwarded by expedited means to the Sponsor's PV; see Section 9.6.1.2.6);
- check for the occurrence of AEs/SAEs since the last study visit; for events exempted from AE/SAE reporting, see Section 9.6.1.2.6);
- ~~perform ABI (or TBI for non-compressible tibial arteries);~~

- QoL assessment with EQ-5D ~~(this assessment can be performed at either the screening visit or the randomization visit)~~;
- Walking Impairment Questionnaire ~~(this assessment can be performed at either the screening visit or the randomization visit)~~;
- remind patient to return with the study medication and study ASA dispensed bottles at their next visit.

New Text:

9.2.1.2 Randomization visit (RxV): 0-10 days after the qualifying revascularization procedure

After meeting all inclusion criteria and none of the exclusion criteria, eligible patients will be randomized by accessing the IxRS system and receive study medication and study ASA as soon as feasible, but no more than 10 days after the qualifying revascularization procedure. The first dose of study medication should be given immediately, but no more than 24 hours after randomization, if study drug can be safely administered (see Section 7.4). Planned additional treatment with clopidogrel after the qualifying revascularization procedure is allowed at the discretion of the investigator as described in Section 8.1.

The following measures/documentations will be performed at the randomization visit:

- randomization of patient (must be performed prior to all other randomization study visit procedures);
- documentation of the details about the qualifying revascularization and its success;
- If laboratory evaluations have been performed and are available per standard or usual care of the subjects in the recent past that reflect baseline hematologic, glucose metabolic, liver, and renal functions, record the relevant and available indices in the eCRF (HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, ALT(SGPT), AST(SGOT), total bilirubin, hemoglobin, hematocrit, platelet count). The serum creatinine value used to assess eligibility and corresponding eGFR should also be entered;
- dispensing of study medication and study ASA with patient instruction;
- administration of first study medication treatment dose (on-site);
- documentation of any changes in concomitant medication since the last study visit;
- assess vital signs (blood pressure, pulse rate);
- check for the occurrence of study efficacy outcome events since the last study visit (these pre-randomization events should be documented on the outcome pages and forwarded by expedited means to the Sponsor's PV; see Section 9.6.1.3;
- check for the occurrence of study safety outcome events (bleeding events) since the last study visit (these pre-randomization events should be documented on the outcome pages and forwarded by expedited means to the Sponsor's PV; see Section 9.6.1.3);
- check for the occurrence of AEs/SAEs since the last study visit; for events exempted from AE/SAE reporting, see Section 9.6.1.3;

- assess the patient's PAD Symptom Status
(This assessment, as well as the QoL assessment and Walking Impairment Questionnaire, should reflect the time period prior to the qualifying revascularization procedure);
- QoL assessment with EQ-5D;
- Walking Impairment Questionnaire;
- remind patient to return with the study medication and study ASA dispensed bottles at their next visit.

[...]

15.1.2.22 Section 9.2.1.3. Treatment phase: Regular study visits from Visit 1 onwards

Section revised per amendment changes 5, 12, 17 and 19.

Old Text:

[...]

At each on-site visit in the treatment phase ~~visit~~, patients will be asked about the occurrence of potential study efficacy outcome events, bleeding events, and AEs/SAEs.

[...]

The following measures/documentations will be performed at each study visit:

- check for the occurrence of study efficacy outcome events since the last study visit;
- check for the occurrence of bleeding events since the last study visit;
- check for the occurrence of AEs/SAEs since the last study visit (for events exempted from AE/SAE reporting, see Section 9.6.1.2.6);

[...]

- assess vital signs (blood pressure, pulse rate);
- perform ABI (or TBI ~~for non-compressible tibial arteries~~);

[...]

- Walking Impairment Questionnaire (questionnaires should be completed before the other visit procedures);

[...]

~~In addition, duplex ultrasound of the treated limb(s) may be performed at one (Visit 1) and 6 months (Visit 3) after randomization (at selected sites only; see Appendix 16.1).~~

New Text:

[...]

At each on-site visit in the treatment phase, patients will be asked about the occurrence of potential study efficacy outcome events, bleeding events, and AEs/SAEs.

[...]

The following measures/documentations will be performed at each study visit:

- check for the occurrence of study efficacy outcome events since the last study visit;
- check for the occurrence of bleeding events since the last study visit;
- Complete all eCRF outcome event, bleeding event and Health Care Resource Utilization (HCRU, see section 9.7.3) pages if applicable
- check for the occurrence of AEs/SAEs since the last study visit (for events exempted from AE/SAE reporting, see Section 9.6.1.3;

[...]

- Assess the patient's PAD Symptom Status;
- If the following laboratory evaluations have been performed since the last study visit and are available in the medical record, it is requested that this information be recorded in the eCRF: HbA1c, creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, ALT(SGPT), AST(SGOT), total bilirubin, hemoglobin, hematocrit, platelet count;

[...]

- Walking Impairment Questionnaire (questionnaires should be completed before the other visit procedures);
- assess vital signs (blood pressure, pulse rate);
- perform ABI (or TBI);

[...]

15.1.2.23 Section 9.2.1.4. End of treatment (EOT) visit

Section revised per amendment changes 5, 12 and 17.

Old Text:

[...]

Likewise, an EOT visit should be performed in those patients who ~~will~~ leave the study permanently in spite of any attempts to hold the patient on study observation (see Section 6.3.1).

[...]

- documentation of any changes in concomitant medication since the last study visit;
- ~~assess vital signs (blood pressure, pulse rate);~~
- ~~perform ABI (or TBI for non-compressible tibial arteries);~~

- QoL assessment with EQ-5D (questionnaires should be completed before the other visit procedures);
- Walking Impairment Questionnaire (questionnaires should be completed before the other visit procedures);
- collect study medication and study ASA bottles dispensed at the previous visit and count and document number of returned tablets. Document any treatment interruptions, if applicable;

[...]

New Text:

[...]

Likewise, an EOT visit should be performed in those patients who leave the study permanently in spite of any attempts to hold the patient on study observation (see Section 6.3.1).

[...]

- documentation of any changes in concomitant medication since the last study visit;
- Assess the patient's PAD Symptom Status;
- QoL assessment with EQ-5D (questionnaires should be completed before the other visit procedures);
- Walking Impairment Questionnaire (questionnaires should be completed before the other visit procedures);
- assess vital signs (blood pressure, pulse rate);
- perform ABI (or TBI);
- collect study medication and study ASA bottles dispensed at the previous visit and count and document number of returned tablets. Document any treatment interruptions, if applicable;

[...]

15.1.2.24 Section 9.3.3. Definition of qualifying revascularization procedure

Section revised per amendment changes 4, 6, 7, 14 and 17.

Old Text:

For the purposes of the current study, the qualifying revascularization procedure (surgical or endovascular) must be technically successful and hemostasis must be assured ~~prior to randomization~~.

~~The qualifying revascularization procedure for patients that require multiple attempts at revascularization on the index leg and lesion must be the last of the planned/foreseeable revascularizations.~~

Surgical procedure: surgical bypass procedures in the lower extremity for PAD ~~below the inguinal ligament~~. This can include a variety of bypass conduit materials and extra-anatomic operations.

Endovascular procedure: catheter-based procedures and hybrid procedures (those procedures involving aspects of both endovascular and surgical revascularizations). The details about the qualifying revascularization procedure will be recorded at the ~~screening~~ visit in the eCRF.

Successful procedure: the qualifying revascularization (regardless of type of procedure) procedure must be deemed technically successful by meeting the following criteria:

- technical success of the procedure with no immediate plan for re-intervention and per the investigator's discretion, the patient can safely be placed on an anticoagulant at the time of randomization;
- demonstrated graft or vascular patency of the qualifying revascularization procedure ~~immediately~~ prior to ~~the time of~~ randomization.

New Text:

For the purposes of the current study, the qualifying revascularization procedure (surgical or endovascular) must be a technically successful procedure in the past 10 days and hemostasis must be assured.

Patients under consideration for this trial may have a treatment plan that focuses on a single procedure or staged procedures where not all revascularizations will necessarily be completed at one time. Preferably, the qualifying revascularization should be the last planned procedure.

Surgical procedure: surgical bypass procedures in the lower extremity for PAD distal to the external iliac artery. This can include a variety of bypass conduit materials and extra-anatomic operations.

Endovascular procedure: catheter-based procedures distal to the external iliac artery and hybrid procedures (those procedures involving aspects of both endovascular and surgical revascularizations).

The details about the qualifying revascularization procedure will be recorded at the randomization visit in the eCRF.

Successful procedure: the qualifying revascularization (regardless of type of procedure) procedure must be deemed technically successful by meeting the following criteria:

- technical success of the procedure with no immediate plan for re-intervention and per the investigator's discretion, the patient can safely be placed on an anticoagulant at the time of randomization;
- demonstrated graft or vascular patency of the qualifying revascularization procedure prior to randomization. Graft or vascular patency is at the discretion of the investigator and can be demonstrated by a variety of means including imaging, hemodynamic and/or physical findings.

15.1.2.25 Section 9.4.1 Assessments and procedures at occurrences of primary efficacy events

Section revised per amendment change 23.

Old Text:

[...]

The analysis of study efficacy outcome events will be based on events as adjudicated by the ICAC. Thus, the occurrence of study efficacy outcome events must be reported on Outcome/CV Event reporting forms and will undergo adjudication by the ICAC.

[...]

New text

[...]

The analysis of study efficacy outcome events will be based on events as adjudicated by the ICAC. Thus, the occurrence of study efficacy outcome events must be reported on Outcome/CV Event reporting forms and will undergo adjudication by the ICAC. All potential coronary ischemic events, cerebrovascular events and peripheral ischemic events should also be reported on the Outcome/CV Event reporting forms.

[...]

15.1.2.26 Section 9.4.2 Definition of study outcome events

Section revised per amendment change 24.

Old Text:

[...]

Ischemic stroke: the definition of ischemic stroke will be an acute episode of neurological dysfunction caused by focal or global brain vascular injury and includes ~~ischemic~~ stroke, ~~hemorrhagic stroke, and undetermined stroke~~. This includes fatal and non-fatal strokes. ~~In case signs and symptoms resolve in less than 24 hours, confirmation of stroke requires neuroimaging evidence of acute brain ischemia (i.e., TIA with positive neuroimaging).~~

[...]

Cardiovascular (CV) death: all deaths will be assumed CV in nature unless a non-CV cause can be clearly shown.

Acute limb ischemia (ALI): for the current study, ALI is defined as clinical history and presentation consistent with a sudden significant worsening of limb perfusion and ~~either~~

- ~~Clinical history including~~ a new pulse deficit with associated rest pain, pallor, paresthesia, or paralysis

~~AND~~

  - confirmation of arterial obstruction by imaging, limb hemodynamics, intraoperative findings, or pathological evaluation

OR

- requiring thrombolysis, thrombectomy, or urgent ~~bypass~~.

[...]

~~Additonal standard definitions~~ for these efficacy outcomes will be provided in a separate ICAC ~~manual~~.

New text

[...]

Ischemic stroke: the definition of ischemic stroke will be an acute episode of neurological dysfunction caused by focal or global brain vascular injury and includes <u>all</u> stroke<u>s</u> that are <u>not of a primary hemorrhagic etiology</u>. This includes fatal and non-fatal strokes.

Cardiovascular (CV) death: all deaths will be assumed CV in nature unless a non-CV cause can be clearly shown.

Acute limb ischemia (ALI): for the current study, ALI is defined as clinical history and presentation consistent with a sudden significant worsening of limb perfusion <u>requiring hospitalization</u> and

- a new pulse deficit with associated rest pain, pallor, paresthesia, or paralysis <u>and either</u>
  - confirmation of arterial obstruction by imaging, limb hemodynamics, intraoperative findings, or pathological evaluation

OR

  - requiring thrombolysis, thrombectomy, or urgent revascularization.

Major amputation due to a vascular etiology: for the current study, this is operationally defined as above-the-ankle amputation that is:

- non-traumatic

AND

- due to a vascular etiology which includes worsening perfusion of the limb but excludes foot sepsis as the primary indication for amputation.

<u>Detailed</u> definitions for these efficacy outcomes <u>are</u> provided in a separate ICAC <u>charter.</u>

15.1.2.27 Section 9.4.3.2. Secondary efficacy variables

Section revised per amendment change 8.

Old Text:

The secondary efficacy variables of the study are:

- time from randomization to the first occurrence of an index limb revascularization;

[...]

New Text:

The secondary efficacy variables of the study are:

- time from randomization to the first occurrence of an index limb revascularization (subsequent index leg revascularization that was not planned or considered as part of the initial treatment plan at the time of randomization);

[...]

15.1.2.28 Section 9.4.3.3. Other efficacy variables

Section revised per amendment changes 8 and 13.

Old text:

Other efficacy variables of the study are:

- time from randomization to the first occurrence of all limb revascularizations of the lower extremity;

[...]

New Text:

Other efficacy variables of the 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;

[...]

- serial changes in limb hemodynamics (ABI/TBI).

15.1.2.29 Section 9.6.1.2.6. Intensity (*section added*)

Section revised per amendment change 16.

New Text:

9.6.1.2.6 Intensity

The intensity of an AE is to be classified according to the following categories:

- mild,
- moderate,
- severe.

15.1.2.30 Section 9.6.1.3.1. Assessment of bleeding events

Section revised per amendment change 17.

Old Text:

[...]

Bleeding occurring after randomization that is related to the index revascularization procedure (e.g. bleeding requiring an unplanned surgical take-back operation to manage will also be reported), including details of the management of the bleeding event and any limb complications (e.g., resulting in major amputation or compartment syndrome requiring surgical management).

[...]

New text

[...]

Bleeding occurring after randomization that is related to the index revascularization procedure (e.g. bleeding requiring an unplanned surgical take-back operation to manage) will also be reported, including details of the management of the bleeding event and any limb complications (e.g., resulting in major amputation or compartment syndrome requiring surgical management).

[...]

15.1.2.31 Section 9.6.1.3.2. Assessment and documentation of adverse events

Section revised per amendment change 17.

Old text:

The investigator has to record on the respective eCRF pages all AEs occurring in the period between the signing of the ICF and the end of the follow-up phase (i.e., post-study treatment follow-up visit by phone at 4 weeks after the EOT visit); after the end of the follow-up phase there is no requirement to actively collect AEs including deaths. In case of permanent discontinuation of study medication, AEs other than outcome events must be reported up to one month after the last dose of study medication intake.

[...]

In the current study, a targeted approach will be followed for AE/SAE documentation and reporting. ~~As regards~~ non-serious AEs, this basically means that only

[...]

New text:

The investigator has to record on the respective eCRF pages all AEs occurring in the period between the signing of the ICF and the end of the follow-up phase (i.e., post-study treatment follow-up visit by phone at 4 weeks after the EOT visit) according to the guidelines in Sections 9.6.1.3.2 and 9.6.1.3.3; after the end of the follow-up phase there is no requirement to actively collect AEs including deaths. In case of permanent discontinuation of study medication, AEs other than outcome events must be reported up to one month after the last dose of study medication intake.

[...]

In the current study, a targeted approach will be followed for AE/SAE documentation and reporting. Regarding non-serious AEs, this basically means that only

[...]

15.1.2.32 Section 9.6.3 Further safety

Section revised per amendment change 19

[...]

Added text:

It is also generally expected that study visit assessments of subjects occurs under the direct supervision of medically qualified personnel such as a physician to determine the need for additional evaluations. It is expected that laboratory surveillance should follow standard of care, tailored to the specific need and clinical indications of the subjects. As part of standard in-hospital, perioperative, and chronic care of such patients with known cardiovascular or other significant medical conditions, repeat and in some cases frequent laboratory testing may be required as part of this standard care. Record the relevant laboratory parameters on the corresponding eCRFs.

15.1.2.33 Section 9.7.1 European Quality of Life-5 Dimensions Questionnaire

Section revised per amendment change 17.

Old text:

[...]

The EQ-5D will be administered at ~~either the screening visit or~~ the randomization visit, and subsequently at each on-site visit.

New text:

[…]

The EQ-5D will be administered at the randomization visit, and subsequently at each on-site visit.

15.1.2.34 Section 9.7.2 Walking Impairment Questionnaire

Section revised per amendment change 17.

Old text:

[…]

Assessments will be performed at ~~either the screening visit or~~ the randomization visit, and subsequently at each on-site visit.

New text:

[…]

Assessments will be performed at the randomization visit, and subsequently at each on-site visit.

15.1.2.35 Section 9.7.3 Health resource use

Section revised per amendment change 17.

Old Text:

Health care resource utilization data related to all efficacy and safety outcomes events (PRO) will be collected for all patients during the study.

[…]

New text:

Health care resource utilization data related to all efficacy and safety outcomes events referred to as Health Care Resource Utilization (HRCU) will be collected for all patients during the study using the Health Care Resource Utilization form in the eCRF.

15.1.2.36 Section 9.7.4. PAD Symptom Status (*section added*)

Section revised per amendment change 12.

Added Text:

The PAD Symptom Status assessment is a graded scale used to assess the severity of chronic PAD. This assessment tool, adapted from the commonly-used Rutherford classification of chronic limb ischemia (Rutherford et al. 1997), categorizes subjects' condition into one of six strata of chronic limb ischemia severity ranging from asymptomatic to tissue loss beyond the digits of the foot. This assessment will be completed by the investigator at the Randomization visit, and subsequently at each on-site visit.

15.1.2.37 Section 10.4. Determination of sample size

Section revised per amendment change 17

Old text

[...]

Inherently, the number of patients enrolled may be adjusted based on the observed overall event rate of the primary efficacy outcomes during the study.

New text

[...]

Inherently, the number of patients enrolled may be adjusted based on the observed overall event rate of the primary efficacy outcomes during the study. Sample size estimation was based on PASS 11 [Hintze 2011].

15.1.2.38 Section 11.1. Data recording

Section revised per amendment change 16 and 17.

Old text

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE~~, which Bayer has licensed~~ from Medidata Solutions. ~~Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies.~~ RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. ~~Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.~~

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All ~~internal Bayer and external investigator site~~ personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in ~~Bayer's~~ clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

~~The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator's site and at Bayer.~~ Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

New text

Data required according to this protocol will be recorded by trained investigational site personnel via data entry into the internet based validated EDC software system RAVE from Medidata Solutions. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All study personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

Sites must implement processes to ensure that all data entered into the eCRF are supported by source documentation. A source document checklist will be used at the site to identify the source data for all data points collected, in accordance with the latest version of the protocol and study agreements. ~~The investigator or the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.~~

New text

Source documentation

Sites must implement processes to ensure that all data entered into the eCRF are supported by source documentation. A source document checklist will be used at the site to identify the source data for all data points collected, in accordance with the latest version of the protocol and study agreements.

15.1.2.39 Section 13.2. Funding and financial disclosure

Section revised per amendment change 17.

Old text

This study will be funded by the Sponsor Bayer HealthCare ~~Inc.~~ and Janssen Pharmaceuticals Inc.

New text

This study will be funded by the Sponsor Bayer HealthCare AG and Janssen Pharmaceuticals Inc.

15.1.2.40 Section 14. Reference list

Section revised per amendment change 12.

Added Text:

Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. Journal of Vascular Surgery. 1997; 26(3):517-38.

Hintze J. Using PASS 11, LLC. Kaysville, Utah, USA. Available: www.ncss.com. 2011.

15.1.2.41 Section 16 Appendices

Section revised per amendment change 25.

Old text:

16.1 Vascular ultrasound substudy

~~Based on the scientific understanding of arterial remodeling and associated increased thrombotic risk after surgical and endovascular therapy, rivaroxaban has the potential to reduce the incidence of atherothrombosis and stenosis in grafts and endovascular revascularization patients. Short and long-term success in lower extremity revascularization is ideally assessed using non-invasive imaging. Vascular ultrasound is an ideal, portable, and widely available noninvasive technique to assess surgical graft patency as well as assess graft lumen diameter.~~

~~An ultrasound substudy of the treated leg may be performed at select qualified sites (at 30 days [Visit 1] and 6 months [Visit 3]) to measure lumen diameter and vessel patency in order to understand the mechanistic effects of study treatment. For additional information, please refer to the applicable ultrasound study manual.~~

New text

Section 16 was deleted.

15.2 Amendment 5

Amendment 5 is the second global amendment to the original clinical study protocol 17454 Version 1.0, dated 23 March 2015.

15.2.1 Overview of changes to the study

15.2.1.1 Change 1: Change of sponsorship information

Rationale:
The sponsor was changed from Bayer Healthcare AG to Bayer AG for non-US territory and sponsor information for Bayer HealthCare Pharmaceuticals Inc. was added for US-territory. Bayer HealthCare AG merged with Bayer AG, an affiliated company within the Bayer Group, effective as of 1st July 2016. Thereby, Bayer HealthCare AG ceased to exist and Bayer AG became its legal successor and automatically took over all of the Bayer HealthCare AG's rights, obligations and liabilities by law. As a result of the above mentioned merger, Bayer AG assumes the role of the sponsor.

Affected sections: Title Page

15.2.1.2 Change 2: Further specification of secondary objective concerning risk of index limb revascularization

Rationale: The secondary endpoints were reordered to reflect clinical relevance. The wording of the secondary endpoint that now becomes the second ordered secondary endpoint has been modified for clarity to reflect the accommodation of a treatment plan for the qualifying revascularization to include the option of a staged procedure plan.

Affected sections: Synopsis, Section 4. Study objectives, Section 9.4.3.2 Secondary efficacy variables

15.2.1.3 Change 3: Changes to exclusion criteria concerning DAPT

Rationale: To adapt to emerging trends in practice patterns across the world and to allow for the inclusion of newer devices and procedures now available.

Affected sections: Synopsis, Section 6.2 Exclusion criteria, Section 8.1 Prior and concomitant therapy

15.2.1.4 Change 4: Amendment of definitions for Endovascular procedure and Surgical procedure

Rationale: Wording of endovascular and surgical procedure definitions modified for clarity to better reflect the definition of hybrid procedures and to make clearer that surgical procedures also include other open procedures such as endarterectomy.

Affected sections: Definitions and medical terms, Section 9.3.3 Definition of qualifying revascularization procedure

15.2.1.5 Change 5: Addition of requirement that ABI/TBI assessments done after consenting must be performed per ABI/TBI Site Manual

Rationale: Added for consistency such that all procedures done after signing of the informed consent and thereafter conform to the same guidelines.

Affected sections: Section 9.1 Tabular schedule of evaluations, Section 9.2.1.1 Screening Visit (ScV): 30 days before, or up to 10 days after qualifying revascularization procedure

15.2.1.6 Change 6: Addition of possible requirement for submission of source documents from the qualifying revascularization procedure for central data verification

Rationale: To allow for the possible collection of source data.

Affected sections: Section 9.3.3 Definition of qualifying revascularization procedure

15.2.1.7 Change 7: Text amendments for clarity and consistency

Rationale: Changes were made to ensure clarity and consistency throughout the document. These changes do not affect the overall study concept. In addition, minor corrections were made as requested through the Note to File attached to the Protocol Amendment 4 (dated 10 FEB 2016).

Affected sections: Synopsis, Section 6.2 Exclusion criteria, Section 7.3 Treatment assignment, Section 9.1 Tabular schedule of evaluations, Section 9.4.1 Assessments and procedures at occurrence of primary efficacy events, Section 9.6.1.3.3 Reporting of serious adverse events and study-specific exemptions

15.2.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol, Version 1.0. In the display of modifications, the "old text" refers to the protocol version preceding this amendment; deletions are ~~crossed out~~. Additions are underlined in the "new text" or "added text."

15.2.2.1 Title Page

The title page was modified based on amendment change 1.

Old text:

Clinical study phase:	3	Date:	~~10 FEB 2016~~
Registration:	EudraCT: 2014-005569-58	Version no.:	~~2.0~~
Sponsor's study no.:	BAY 59-7939 / 17454		
Sponsor:	Bayer ~~HealthCare~~ AG, D-51368 Leverkusen, Germany		

New text:

[…]

Clinical study phase:	3	Date:	21 MAR 2017
Registration:	EudraCT: 2014-005569-58	Version no.:	3.0
Sponsor's study no.:	BAY 59-7939 / 17454		
Sponsor:	Non-US territory: Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA		

[…]

15.2.2.2 Synopsis

This section was modified based on amendment changes 2, 3 and 7.

Old text:

[…]	
Background treatment	All study patients will receive treatment with open label ASA 100 mg orally once daily (od) during the entire course of the study; additional treatment with clopidogrel may be administered for a planned duration of up to 30 days ~~following~~ after the qualifying revascularization procedure ~~(or up to 60 days for a labeled indication [e.g. drug coated stent or balloon]), at the discretion of the investigator.~~
[…]	
Diagnosis and main criteria for inclusion/exclusion	[…] Main exclusion criteria are: • […] • Planned dual anti-platelet therapy (DAPT) use for the qualifying revascularization procedure of clopidogrel in addition to ASA for ~~>30 days~~ after the qualifying revascularization procedure ~~(or > 60 days for a labeled indication [e.g. drug coated stent or balloon]) (*Planned use of clopidogrel not exceeding 60 days for a labeled indication for a device [e.g., stent or balloon] may be allowed; see section 8.1 for further guidance on clopidogrel)~~ • Planned ~~DAPT~~ use ~~for~~ any other ~~indication(s) with any P2Y12 antagonists in addition to ASA~~ after the qualifying revascularization procedure.
[…]	

New text (incl. changed sequence of bullet points for objectives and variables):

[…]	
Study objective(s)	[…] Secondary efficacy objectives: • 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
[…]	
Background treatment	All study patients will receive treatment with open label ASA 100 mg orally once daily (od) during the entire course of the study; additional treatment with clopidogrel may be administered for a planned duration of up to 30 days after the qualifying revascularization procedure (or up to 6 months for complex procedures or devices in the investigator's opinion that require longer use); it is strongly recommended that any course of clopidogrel is kept to the minimum necessary in accordance with local standard of care and international practice guidelines (typically 30 days, or up to 60 days for some drug-coated products or devices)(*see section 8.1for further guidance on clopidogrel*).
[…]	
Diagnosis and main criteria for inclusion/exclusion	[…] Main exclusion criteria are: • patients undergoing revascularization for asymptomatic PAD or mild claudication without functional limitation of the index leg, • […] • Planned dual antiplatelet therapy (DAPT) use for the qualifying revascularization procedure of clopidogrel in addition to ASA for >6 months after the qualifying revascularization procedure; it is strongly recommended that any course of clopidogrel is kept to the minimum necessary in accordance with local standard of care and international practice guidelines (typically 30 days, or up to 60 days for some drug-coated products or devices), and is only allowed for up to 6 month for complex procedures or devices that in the investigator's opinion require longer use; see section 8.1 for further guidance on clopidogrel. • Planned use of any additional antiplatelet agent other than

	clopidogrel and ASA after the qualifying revascularization procedure.
[…]	
Primary and secondary variable(s)	[…] The secondary efficacy variables of the study will be: • 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 revascularizations 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 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 venous thromboembolic (VTE) events;
[…]	

15.2.2.3 Definitions and medical terms

This section was modified based on amendment change 4.

Old text:

[…]	
Endovascular procedure	Refers to **c**atheter-based and hybrid procedures (those procedures involving aspects of both endovascular and surgical revascularizations) for PAD ~~distal to the external iliac artery~~.
[…]	
Surgical procedure	Refers to surgical ~~bypass~~ procedure in the lower extremity for PAD ~~distal to the external iliac artery~~. This can include a variety of bypass conduit materials and extra-anatomic operations.

New text:

[…]	
Endovascular procedure	Refers to **c**atheter-based and hybrid procedures (those procedures involving aspects of both endovascular and surgical revascularizations) for PAD.
[…]	

Surgical procedure	Refers to open surgical procedure in the lower extremity for PAD. This can include a variety of procedures, bypass conduit materials, and extra-anatomic operations.

15.2.2.4 Section 4. Study objectives

This section was modified based on amendment change 2.

New text (incl. changed sequence of bullet points):

The secondary efficacy objectives of the study 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.

15.2.2.5 Section 6.2 Exclusion criteria

This section was modified based on amendment changes 3 and 7.

Old text:

[…]

7. Planned dual antiplatelet therapy (DAPT) use for the qualifying revascularization procedure of clopidogrel in addition to ASA for >~~30 days*~~ after the qualifying revascularization procedure ~~(or > 60 days for a labeled indication [e.g.drug coated stent or balloon])~~

~~(*Planned use of clopidogrel not exceeding 60 days for a labeled indication for a device [e.g., stent or balloon] may be allowed; see section 8.1 for further guidance on clopidogrel)~~

8. Planned* ~~DAPT~~ use ~~for~~ any other ~~indication(s) with any P2Y12 antagonists (e.g. percutaneous coronary interventions) in addition to ASA~~ after the qualifying revascularization procedure
(**This exclusion criterion refers to the clinical condition at the time of randomization. The use of DAPT with ASA plus ~~P2Y12 antagonists of any type~~ for new indication(s) occurring after randomization is permitted~~; see Section~~ 7.4.4*);

[..]

11. Systemic treatment with strong inhibitors of both Cytochrome P450 isoenzyme 3A4 (CYP3A4) and p-glycoprotein (P-gp) inhibitors (e.g., systemic azole antimycotics, such as ketoconazole [fluconazole is permitted], and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir), or strong inducers of CYP3A4 (e.g., rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine) ~~at the time of screening or their~~ anticipated ~~use~~ during the study.

- Exclusion criteria related to bleeding risks or systemic conditions:

[…]

14. ~~Medical history of chronic renal failure, any~~ condition requiring dialysis or renal replacement therapy or a renal impairment at screening assessed with an estimated glomerular filtration rate <15 mL/min/1.73 m^2*
(**if a patient's eGFR is <30 mL/min/1.73 m^2 prior to the procedure, it must remain to be >15 mL/min/1.73 m^2 72 hours after the procedure to enroll and randomize the patient*);

New text:

[…]

7. Planned dual antiplatelet therapy (DAPT) use for the qualifying revascularization procedure of clopidogrel in addition to ASA for >6 months after the qualifying revascularization procedure; it is strongly recommended that any course of clopidogrel is kept to the minimum necessary in accordance with local standard of care and international practice guidelines (typically 30 days, or up to 60 days for some drug-coated products or devices) and is only allowed for up to 6 months for complex procedures or devices in the investigator's opinion that require longer use; see section 8.1 for further guidance on clopidogrel.

8. Planned* use of any additional antiplatelet agent other than clopidogrel and ASA after the qualifying revascularization procedure
(**This exclusion criterion refers to the clinical condition at the time of randomization. The use of DAPT with ASA plus clopidogrel, for new indication(s) occurring after randomization is permitted*)

[…]

11. Systemic treatment with strong inhibitors of both Cytochrome P450 isoenzyme 3A4 (CYP3A4) and p-glycoprotein (P-gp) inhibitors (e.g., systemic azole antimycotics, such as ketoconazole [fluconazole is permitted], and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir), or strong inducers of CYP3A4 (e.g., rifampicin,

rifabutin, phenobarbital, phenytoin and carbamazepine) anticipated after randomization or during the study.

- Exclusion criteria related to bleeding risks or systemic conditions:

[…]

14. Any condition requiring dialysis or renal replacement therapy, or a renal impairment at screening assessed with an estimated glomerular filtration rate <15 mL/min/1.73 m^2* (**if a patient's eGFR is <30 mL/min/1.73 m^2 prior to the procedure, it must remain to be >15 mL/min/1.73 m^2 72 hours after the procedure to enroll and randomize the patient*);

15.2.2.6 Section 7.3 Treatment assignment

This section was modified based on amendment change 7.

New text:

[…]

The clopidogrel use defining the randomization strata refers to actual clopidogrel use, at randomization, as adjunct treatment for the qualifying revascularization. Specific procedures for treatment assignment through the IxRS will be described in the IxRS manual.

15.2.2.7 Section 8.1 Prior and concomitant therapy

This section was modified based on amendment change 3.

Old text:

[…]

If deemed required by the investigator, the use of clopidogrel ~~for a planned duration~~ of ~~up~~ to 30 days ~~following the qualifying revascularization procedure~~, or ~~planned duration of~~ up to 60 days ~~in the case of a labeled indication for a device (e.g.~~ drug-coated ~~stent~~ or ~~balloon), is allowed. Justification will need to be documented during the course of this planned use of clopidogrel if the investigator determines that a medical need arises that warrants that clopidogrel be administered for >30 days following the qualifying revascularization, or >60 days in the case of a device~~. Clopidogrel will not be supplied as a study medication.

[…]

New text:

[…]

If deemed required by the investigator, the use of clopidogrel concomitantly with study drugs is allowed at the time of randomization. It is strongly recommended that any course of clopidogrel is kept to the minimum necessary to comply with local standard of care and international practice guidelines (typically 30 days, or up to 60 days for some drug-coated products or devices). Clopidogrel will not be supplied as a study medication.

[…]

15.2.2.8 Section 9.1 Tabular schedule of evaluations

This section was modified based on amendment changes 5 and 7.

New text:

Table 9–1: Schedule of assessments - amended

Timelines	ScV [a]	Qualifying revascular-ization (Rev)	RxV [a] (T0)	Treatment Phase						PS-FU 1 Mo post EOT
				V1	V2	V3	V4	V5-Vx	EOT visit [b]	
				1 Mo	3 Mo	6 Mo	12 Mo	every 6 Mo		
Visit Window (weeks if not otherwise specified)	-30 days before, to +10 days after, Rev		Up to +10 days after Rev	±10 days	±4	±4	±4	±4		±1
Type of Visit	Visit		Visit	Visit	Visit	Visit	Visit	Visit	Visit	☎
[…]										
ABI/TBI[h]	● [g]			●	●	●	●	●	●	
[…]										

[…]
f: Only AE/ SAEs not exempted from adverse event reporting and specified in the protocol need to be documented (see Section 9.6.1.3 (change no.17).
g: ABI/TBI values used at screening may be historical (captured in the patient's medical history), but must not be older than 12 months prior to the qualifying revascularization procedure (*change no. 5*). If an ABI/TBI is performed during screening to assess eligibility, it must be completed prior to, or at the time of, the qualifying revascularization (*change no. 6*).
h: ABI/TBI assessments performed after informed consent is obtained must be performed per the guidance in the ABI/TBI Site Manual.

15.2.2.9 Section 9.2.1.1 Screening Visit (ScV): 30 days before, or up to 10 days after qualifying revascularization procedure

This section was modified based on amendment change 5.

New text:

- […]
- perform ABI (or TBI) if no ABI/TBI data are available for the patient within the last 12 months prior to the qualifying revascularization; ABI/TBI assessments performed after informed consent is obtained must be performed per the guidance in the ABI/TBI Site Manual.

15.2.2.10 Section 9.3.3 Definition of qualifying revascularization procedure

This section was modified based on amendment changes 4 and 6.

Old text:

For the purposes of the current study, the qualifying revascularization procedure (surgical or endovascular) must ~~be~~ a technically successful procedure in the past 10 days, and hemostasis must be assured.

[…]

Surgical procedure: surgical ~~bypass~~ procedures in the lower extremity for PAD ~~distal to the external iliac artery~~. This can include a variety of bypass conduit materials and extra-anatomic operations.

Endovascular procedure: catheter-based procedures ~~distal to the external iliac artery~~ and hybrid procedures (those procedures involving aspects of both endovascular and surgical revascularizations).

[…]

New text:

For the purposes of the current study, the qualifying revascularization procedure (surgical or endovascular) must include a technically successful procedure distal to the external iliac artery in the past 10 days, and hemostasis must be assured.

[…]

Surgical procedure: open surgical procedures in the lower extremity for PAD. This can include a variety of procedures, bypass conduit materials, and extra-anatomic operations.

Endovascular procedure: catheter-based procedures and hybrid procedures (those procedures involving aspects of both endovascular and surgical revascularizations) for PAD.

[…]

Sites may be required to submit source documents from the qualifying revascularization procedure for central data verification.

15.2.2.11 Section 9.4.1 Assessments and procedures at occurrence of primary efficacy events

This section was modified based on amendment change 7.

New text:

The analysis of study efficacy outcome events will be based on events as adjudicated by the ICAC. Thus, the occurrence of study efficacy outcome events must be reported on Outcome/CV Event reporting forms, as described in the Endpoint Event Site Manual, and will undergo adjudication by the ICAC. All potential coronary ischemic events, cerebrovascular events and peripheral ischemic events should also be reported on the Outcome/CV Event reporting forms.

15.2.2.12 Section 9.4.3.2 Secondary efficacy variables

This section was modified based on amendment change 2.

New text (incl. changed sequence of bullet points):

The secondary efficacy variables of the 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 venous thromboembolic (VTE) events.

15.2.2.13 Section 9.6.1.3.3 Reporting of serious adverse events and study-specific exemptions

This section was modified based on amendment change 7.

Old text:

[…]

2. **Safety outcome events** (i.e., bleeding events occurring after ~~randomization~~) will not be recorded on the AE page and not be reported as SAEs to Sponsor's PV department, but they will be collected on the specific eCRF pages as a safety outcome event.

[…]

New text:

[…]

2. **Safety outcome events** (i.e., bleeding events occurring after signing of the ICF) will not be recorded on the AE page and not be reported as SAEs to Sponsor's PV department, but they will be collected on the specific eCRF pages as a safety outcome event.

[…]