



Cover Page

This supplement contains the following items:

1. Version 1.0 of NAVIGATE ESUS Clinical Study Protocol (2014-07-16) – Original Protocol
2. Version 2.0 of NAVIGATE ESUS Clinical Study Protocol (2015-11-05) – Final Protocol
3. Summary of revisions
4. Version 1.0 of NAVIGATE ESUS Statistical Analysis Plan (2015-03-02) – Original Statistical Analysis Plan
5. Version 3.0 of NAVIGATE ESUS Statistical Analysis Plan (2017-12-20) – Final Statistical Analysis Plan
6. Summary of revisions

Title page

Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS), comparing rivaroxaban 15 mg once daily with aspirin 100 mg (NAVIGATE ESUS)

Secondary prevention of stroke in patients with a recent ESUS

Test drug: BAY 59-7939/rivaroxaban

Clinical study phase: III Date: 16 July 2014

EudraCT no.: 2013-000768-27 Version no.: 1.0

Study no.: BAY 59-7939/16573

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The study will be conducted in compliance with the protocol, International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) and any applicable regulatory requirements.

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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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Synopsis

Title	Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS), comparing rivaroxaban 15 mg once daily with aspirin 100 mg (NAVIGATE ESUS)
Short title	Secondary prevention of stroke in patients with ESUS
Clinical study phase	III
Study objectives	<p>The primary efficacy objective is:</p> <ul style="list-style-type: none"> To evaluate whether rivaroxaban is superior to aspirin in reducing the risk of recurrent stroke and systemic embolism in patients with a recent ESUS <p>The secondary efficacy objective is:</p> <ul style="list-style-type: none"> To evaluate whether rivaroxaban is superior to aspirin in reducing cerebrovascular events, cardiovascular events, and mortality in patients with a recent ESUS <p>The safety objective is to document the incidence of clinically relevant bleeding</p>
Study medication	Rivaroxaban 15 mg (immediate-release film-coated tablets), or Aspirin 100 mg (enteric-coated tablets)
Type of control	Double dummy: Matching placebo will be provided for rivaroxaban and aspirin
Route of administration	Study medication is administered orally once daily and should be taken with food
Indication	Secondary prevention of stroke and prevention of systemic embolism in patients with a recent ESUS
Diagnosis and main criteria for inclusion	<p>Recent ESUS (between 7 days and 6 months), defined as:</p> <ul style="list-style-type: none"> Recent ischemic stroke (including transient ischemic attack with positive neuroimaging) visualized by brain imaging that is not lacunar, and Absence of cervical carotid atherosclerotic stenosis $\geq 50\%$ or occlusion, and No atrial fibrillation after ≥ 24-hour cardiac rhythm monitoring, and No intra-cardiac thrombus on transthoracic echocardiography, and No other specific cause of stroke (for example, arteritis, dissection, migraine/vasospasm, drug abuse)
Study design	Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study

Methodology	<p>Patients who fulfill all inclusion and none of the exclusion criteria after giving informed consent will be randomly allocated 1:1 to either rivaroxaban 15 mg or aspirin 100 mg orally once daily. Randomization will be stratified by country and age <60 and ≥60 years. No more than 10% of the total patient population will be randomized into the age group <60 years.</p> <p>At randomization, patients will receive study medication and instructions for its administration. Thereafter, patients will return to the clinic at 1, 6, and 12 months and then every 6 months until the end of study (efficacy cut-off date) is announced. At 3 months, patients will be contacted by telephone. Throughout the study and at clinic visits, patients will be assessed for efficacy (stroke, systemic embolism, myocardial infarction, cardiovascular death, and all-causes mortality) and safety vital signs, bleeding, serious adverse events which are not outcome events, pregnancies, non-serious adverse events leading to permanent study drug discontinuation, and any non-serious adverse events of particular concern to the investigator).</p> <p>Suspected clinical study outcomes (efficacy and bleeding) will be assessed by an Independent Central Adjudication Committee blinded to treatment allocation. Adjudicated results will be the basis for the final analyses.</p> <p>The study is event-driven and thus, all patients will be treated (or followed-up in case of permanent discontinuation of study medication) until the required approximately 450 confirmed primary efficacy outcomes are expected to have occurred.</p> <p>An Independent Data Monitoring Committee will monitor patient safety during the study and give recommendations to the Steering Committee.</p>
Number of subjects	<p>The study is event-driven and it is estimated that approximately 7000 patients (3500 per treatment group) are to be enrolled in order to have 450 patients experiencing a positively adjudicated primary efficacy outcome event.</p> <p>The number of patients enrolled may be adjusted based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study.</p>
Primary variable	<p>Time from randomization to first occurrence of any of the components of the composite outcome (adjudicated); including:</p> <ul style="list-style-type: none"> • Stroke (ischemic, hemorrhagic, and undefined stroke, transient ischemic attack with positive neuroimaging) • Systemic embolism

Plan for statistical analysis	<p>The primary efficacy analyses will be based on the intent-to-treat population. Rivaroxaban treatment will be compared with the aspirin control 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. Risk reduction will be estimated with the stratified Cox proportional hazards model.</p> <p>Secondary efficacy outcomes will be analyzed using similar methods as for the primary efficacy analysis. Testing will be performed in hierarchical order.</p> <p>There will be 1 formal interim analysis to assess efficacy and stop for overwhelming superiority, which will occur when approximately 67% of the planned primary efficacy outcomes have accrued.</p> <p>The analysis of the safety outcomes will be similar to those described for the primary efficacy outcome.</p>
Anticipated total study duration and study duration per patient	<p>Total study duration: ~3 years Randomization period: ~2 years Treatment duration of last patient randomized: ~1 year Mean treatment duration per patient: ~2 years</p> <p>The study is event driven and these timelines may vary depending on the enrollment rate and event rate in the study.</p>

Table of procedures

	Screen	Random	Treatment Phase						Washout
	V1	V2	V3	V4	V5	V6	V7-V [∞]	EOT ^a	Safety Visit
Timelines	-4 to 0 wks ^b	0	1 Mo	3 Mo	6 Mo	12 Mo	every 6 Mo	End of Treat	1 Mo post EOT
Visit Window (weeks)			±1	±4	±4	±4	±4		±1
Type of Visit	Visit	Visit	Visit	☎	Visit	Visit	Visit	Visit	☎
Initiation procedures									
Informed consent	•								
Eligibility criteria	•								
Demographics	•								
Medical history and stroke risk factors	•								
Treatment and diagnosis of stroke ^c	•								
Pregnancy test ^d	•								
eGFR ^e	•								
Weight/height ^f	•					•	□		
Medication									
ConMeds ^g		•				•	□	•	
1 st study drug		•							
Drug dispense		•			•	•	•	•	
Drug return + accountability		•			•	•	•	•	
Efficacy/Safety Outcomes^h			← continuous reporting →						
Safety			← continuous reporting →						
Adverse events ⁱ									
Vital signs ^j		•			•	•	□	•	
Outcomes Research									
EQ-5D		•			•	•	•	•	
MoCA, DSS, and SAGE		•				•		•	
Modified Rankin Score ^k	•					•		•	

Abbreviations: EOT = end of treatment; Mo = month; V = visit, ☎ = telephone contact; eGFR = estimated glomerular filtration rate; ConMeds = Concomitant medications; MoCA = Montreal Cognitive Assessment; DSS = Digit Symbol Substitution test; SAGE = Standard Assessment of Global-Activities in the Elderly; EQ-5D = European Quality of Life-5 Dimensions questionnaire; SAE = serious adverse event; TIA = transient ischemic attack; MI = myocardial infarction

- a End of treatment visit is to be performed once the patient has permanently discontinued study medication and when no further visits at the site will be performed
- b Screening visit can be the same as randomization visit, if all required tests for eligibility criteria are available at screening visit. Maximum screening period 4 weeks.
- c Acute and chronic therapy of stroke (for example [e.g.], thrombolysis, aspirin [ASA]) and diagnostic tests performed to diagnose acute stroke and Embolic Stroke of Undetermined Source (ESUS) as well as National Institutes of Health Stroke Score (NIHSS)
- d Only in women of childbearing potential (local urine or serum pregnancy test)
- e Creatinine to be measured at the local laboratory at screening, unless conducted within 1 month prior to screening. The eGFR may be recorded as reported by the local laboratory or otherwise should be calculated using Modification of Diet in Renal Disease (MDRD) formula. A calculator may be found at www.mdrd.com.

- During the study creatinine and eGFR should be measured according to local practice.
- f Height to be measured only at screening
 - g Concomitant medications and the changes need to be documented only at the specified visits for chronic cerebro- and cardiovascular treatments. In addition, treatments for SAEs and outcome events must be reported.
 - h All potential outcome events including recurrent stroke, TIA, systemic embolism, MI, hospitalizations for cardiac chest pain, deaths, and bleeding must be reported on an ongoing basis even if the patient is permanently discontinued from study treatment. Healthcare resource use will be documented for all endpoints. See Section 7.6.1.1
 - i Only SAEs not exempted from SAE reporting, pregnancy, non-serious AE leading to permanent discontinuation, and non-serious AEs of particular concern to the investigator need to be reported. See Section 7.5.3.2.
 - j Blood pressure and heart rate
 - k For definition see Section 7.6.1.4. In case of recurrent stroke to be done at 7 days post stroke or at discharge from hospital in case this occurs before 7 days and again at 3 months post stroke
 - To be performed at specified visits
 - To be performed only once per year

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List of abbreviations

ACS	Acute coronary syndrome
AE	Adverse event
AF	Atrial fibrillation
APCC	Activated prothrombin complex concentrate
ARISTOTLE	Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE)
ASA	Acetylsalicylic acid; aspirin
AVERROES	A Phase III Study of Apixaban in Patients With Atrial Fibrillation (AVERROES)
BHC	Bayer HealthCare
b.i.d.	Twice daily
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence interval
ConMed	Concomitant medication
CRO	Contract research organization
CT	Computed tomography
cTn	Cardiac troponin
CV	Cardiovascular
CYP3A4	Cytochrome P450 isoenzyme 3A4
DSS	Digit Symbol Substitution test
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EINSTEIN	Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis -The EINSTEIN DVT Study
e.g.	for example
eGFR	Estimated glomerular filtration rate

ENGAGE	Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (EngageAFTIMI48)
EOT	End-of-treatment
EQ-5D	European Quality of Life-5 Dimensions questionnaire
ESUS	Embolic stroke of undetermined source
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
H	hypothesis
HDPE	High-density polyethylene
HR	Hazard ratio
ICAC	Independent Central Adjudication Committee
ICF	Informed consent form
ICH	International Conference on Harmonisation
IB	Investigator's brochure
i.e.	id est (that is)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	International ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-to-treat
IxRS	Interactive web/voice response system
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction

Mo	Month
MoCA	Montreal Cognitive Assessment
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Score
NSAID	Non-steroid anti-inflammatory drug
NV	Corporation (in The Netherlands)
NVAF	Non-valvular atrial fibrillation
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
o.d.	Once daily
OMP	Ortho McNeil Pharmaceuticals
p	p-value
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PE	Pulmonary embolism
P-gp	P-glycoprotein
PICCS	Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS)
PID	Patient identification
PPS	Per protocol set
PT	Prothrombin time
PV	Pharmacovigilance
QA	Quality assurance
ROCKET AF	An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation
RRR	Relative risk reduction
S	survival
SAE	Serious adverse event

SAF	Safety data set
SAGE	Standard Assessment of Global-Activities in the Elderly
SAP	Statistical analysis plan
SC	Steering Committee
SUSAR	Suspected unexpected serious adverse reaction
TIA	Transient ischemic attack
USA	United States of America
TOAST	Trial of Org 10172 in Acute Stroke Treatment
V	Visit
VKA	Vitamin K antagonist
vs.	versus
VTE	Venous thromboembolism
WARSS	Warfarin-Aspirin Recurrent Stroke Study
WHO	World Health Organization
WMH	White matter hyperintensities

1. Introduction

1.1 Background

Globally, cerebrovascular disease (stroke) is the second leading cause of death (1) and the fourth leading cause of disease burden as measured in disability-adjusted life years. (2) The World Health Organization (WHO) estimates that worldwide 16 million people suffer a first ever stroke annually, with 5 million deaths due to stroke in 2005, and another 5 million left permanently disabled. (3)

The incidence of stroke is declining in many developed countries, largely as a result of better control of high blood pressure and reduced levels of smoking. However, the absolute number of strokes continues to increase because of the ageing population. In the absence of additional population-wide interventions, the numbers are expected to rise to 18 million first-ever strokes and 6.5 million deaths in 2015 and 7.8 million deaths in 2030.

Approximately two-thirds of patients are left with physical or cognitive disabilities. Stroke costs the United States (US) an estimated \$54 billion each year. (4) In the US, 75% of all strokes are first or new strokes and 25% are recurrent strokes. (5)

About 87% of all strokes are of ischemic origin. Sub-types of ischemic stroke are defined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. (6)

Approximately 30% of all ischemic strokes are due to arteriosclerosis of the intra- and extracranial large arteries; 20 % are lacunar, i.e., due to small artery disease; 20% have a cardioembolic source such as atrial fibrillation; and 5% are classified as “unusual” (for example [e.g.], dissections, arteritis). For the remaining 25% of strokes, the term ‘Cryptogenic Stroke’ has been used to describe patients with ischemic stroke in whom there is no clear etiology. (7) In cryptogenic stroke the source of embolism or thrombosis cannot be readily determined in each and every patient, and in fact, it is not uncommon to identify more than one potential cause in the individual patient.

1.2 Embolic stroke of undetermined source

Recently, the concept of “embolic stroke of undetermined source” (ESUS) has developed, recognizing that except for lacunar strokes, most cryptogenic strokes are embolic.(7) The sources of embolism underlying ESUS include the heart (either within the heart or via paradoxical embolism from a venous source), aortic arch, or the large cervical and cerebral arteries.

Investigations to establish a diagnosis of ESUS involves exclusion of lacunar stroke and stroke related to severe occlusive atherosclerotic disease of intra- and extracranial large arteries. Lacunar strokes need to be excluded, as the great majority of these are due to in-situ thrombosis on microatheroma or non-thrombotic occlusions of small cerebral arteries. Newly detected, previously unrecognized, major-risk cardioembolic sources such as atrial fibrillation and left ventricular thrombus that warrant anticoagulation therapy must also be excluded.

In summary, ESUS is defined as a non-lacunar brain infarct without proximal arterial stenosis or major-risk cardioembolic sources that have a clear indication for anticoagulation.

1.3 Studies assessing the efficacy of anticoagulation for secondary prevention of embolic stroke of undetermined source

The only available randomized clinical trial data in patients with cryptogenic stroke stem from a subgroup analysis in the Warfarin-Aspirin Recurrent Stroke Study (WARSS; 1993-2000),⁽⁸⁾ where patients were randomly assigned to aspirin (acetylsalicylic acid; ASA) 325 mg once daily (o.d.) or warfarin (target International Ratio [INR] 1.4 to 2.8). This subgroup included 576 out of the 2206 patients. Cryptogenic stroke was based on the TOAST criteria ⁽⁶⁾ (2 or more causes identified or a negative evaluation, or an incomplete evaluation) ^(7,9). The primary outcome of ischemic stroke or death occurred in 15.0% assigned to warfarin vs. 16.5% assigned to ASA over two years (Hazard Ratio [HR] 0.92, 95% Confidence Interval [CI] 0.6-1.4). ⁽⁹⁾ The INRs achieved were relatively low (median achieved INR = 1.9) and were a noteworthy reflection of the relative efficacy of anticoagulation vs. antiplatelet agents in patients with cryptogenic stroke. The rates of major hemorrhage were low (2.22 per 100 patient-years in the warfarin group and 1.49 per 100 patient-years in the ASA group).

For 338 participants with cryptogenic stroke whose computed tomography (CT) showed an “embolic topography” the 2 year rate of recurrent ischemic stroke or death was 12% with warfarin vs. 18% with ASA (HR=0.66, 95% CI 0.4-1.2). ⁽⁹⁾

In summary, despite a low therapeutic warfarin anticoagulation range (median INR = 1.9) and limited statistical power, WARSS data from a randomized comparison support the concept that anticoagulation may be substantially more efficacious than ASA for patients with cryptogenic ischemic stroke with embolic features (i.e., those comparable to ESUS patients). In addition, in the PICSS study, 260 participants with a patent foramen ovale, the primary outcome (2 year rate of recurrent ischemic stroke or death) was halved in those assigned to warfarin (9% warfarin vs. 17% ASA). ⁽¹⁰⁾

Vitamin K antagonists (VKAs) are not routinely used for cryptogenic stroke/ESUS. A Cochrane Collaboration meta-analysis of trials for secondary prevention in patients with a history of non-cardioembolic stroke of various causes, such as large artery atherosclerosis, intracranial artery stenosis, small penetrating artery disease, and strokes of unknown cause (i.e., cryptogenic stroke) suggested that higher intensity anticoagulation with VKAs could be associated with higher all-cause mortality and major bleeding events. ⁽¹¹⁾

1.4 Efficacy and safety of rivaroxaban in patients with prior stroke

Rivaroxaban is an oral, highly selective direct Factor Xa inhibitor. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi.

Rivaroxaban has been tested in interventional and non-interventional trials involving more than 70,000 patients and the cumulative worldwide exposure during 5.5 years of marketing (since SEP 2008) is estimated at approximately 2.4 million patient years in approximately 8 million patients treated overall. Rivaroxaban is approved in adults for the prevention of venous thromboembolism (VTE) following elective hip or knee replacement surgery, treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE. It has been approved in the European Union (EU) and other countries

for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers when co-administered with ASA or ASA plus clopidogrel or ticlopidine.

Rivaroxaban is also approved for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors. Approval was based on the ROCKET-AF trial, (12) in which rivaroxaban was shown to be non-inferior to warfarin. There was also no significant between-group difference in the risk of major bleeding. A pre-specified subgroup analysis showed that the efficacy and safety of rivaroxaban compared with warfarin among patients with and without a previous transient ischemic attack (TIA) or ischemic stroke was consistent. (13)

A major advantage of the novel oral anticoagulants over warfarin that emerged from recent phase III randomized clinical trials involving non-valvular atrial fibrillation patients is the reduced risk of intracranial hemorrhage. (12,14,15) In the ROCKET-AF trial, intracranial hemorrhage was reduced (HR 0.67; p=0.02) by rivaroxaban relative to warfarin. (12)

Prior stroke is a risk factor for intracerebral hemorrhage during warfarin anticoagulation. In ROCKET-AF, there was no significant interaction between prior stroke and relative effect of rivaroxaban vs. warfarin on hemorrhagic stroke. (13) While patients with recognized AF will be excluded from the proposed trial, the cause of ESUS in many patients is unrecognized cardiogenic embolism, including undiagnosed paroxysmal atrial fibrillation, and hence these observations may be relevant.

Patients with cryptogenic ischemic stroke are likely to have a higher risk of intracranial hemorrhage than patients with vascular disease without prior stroke/TIA. The absolute rate of intracranial hemorrhage in patients with cryptogenic ischemic stroke, if given rivaroxaban, is likely to be less than that observed in ROCKET-AF participants with prior stroke/TIA (0.59%/year). This is due to a lower average age of patients with cryptogenic stroke (a powerful independent risk factor for intracranial hemorrhage [16]) compared with the high risk ROCKET-AF population.

The only large-scale comparison of a novel oral anticoagulant (apixaban) with ASA, the AVERROES study, involving patients with NVAF who were unsuitable to VKA treatment was stopped prematurely by the Independent Data Monitoring Committee (IDMC) for overwhelming efficacy. (17) A significant reduction in the primary efficacy outcome (stroke and systemic embolism) was reported for all patients (HR 0.45) and in the patients with previous stroke or TIA the HR was 0.29. (18) Major bleeding was more frequent in patients with a history of stroke or TIA than in patients without (HR 2.88) but the overall risk for these events was small and only slightly more reported in the apixaban group (44 vs. 39 events, HR 1.13). There was also no difference in intracranial bleeding with apixaban vs. ASA, albeit based on a relatively small number of events (apixaban = 11, ASA = 13). (17) In a recent comprehensive meta-analysis, based on indirect comparison, the risk of subdural hematoma (comprising 30% of intracranial hemorrhages) was equal comparing oral factor Xa inhibitors with ASA. (19) Consequently, intracranial hemorrhage is unlikely to limit a comparison of rivaroxaban with ASA for secondary prevention of stroke in patients with ESUS.

1.5 Current guideline recommendations and dose of aspirin

The 2008 American College of Chest Physicians guideline and 2008 American Heart Association guideline specifically recommended antiplatelet therapy for patients with cryptogenic ischemic stroke. (20, 21) The 2008 European Stroke Organization guideline, the 2014 American Heart Association revised guideline, the 2012 American College of Chest Physicians guideline, and the 2008 Canadian Best Practice Recommendations for Stroke Care do not comment specifically on cryptogenic stroke, but recommend antiplatelet therapy for patients with non-cardioembolic ischemic stroke. (22-25) These are primarily Grade 1A/(Class I, Level of Evidence A) recommendations. Aspirin is the drug most frequently used. A daily dosage range of 50 mg to 325 mg of ASA is recommended in current guidelines, although the data for doses < 75 mg are limited. An ASA dosage of 100 mg daily is included in most major guidelines and is acceptable to most clinicians around the world. Guidelines recommend initiation of ASA immediately after brain imaging has excluded intracerebral hemorrhage, if the patient can swallow, and this is standard of care. The long-term (> 5 years) treatment is recommended. (25)

1.6 Study rationale

Randomized clinical trials have addressed secondary prevention for all major ischemic stroke subtypes except for cryptogenic stroke or ESUS. Among the estimated 300,000 patients with acute cryptogenic stroke annually in North America and Europe there has been little progress in secondary prevention during the past two decades. There is a substantial unmet medical need in this patient population, as despite treatment with antiplatelets, the recurrent stroke rate still remains at 3 to 6% annually. (7)

There is persuasive evidence that the dominant underlying pathophysiology of ESUS is embolism (cardioembolic, arteriogenic, or paradoxical). Improvements in imaging technology and an increased appreciation of the underlying pathophysiology of ESUS have resulted in better understanding and in a practical clinical definition of ESUS (7) so that these patients can be reliably identified.

Based on evidence for superior efficacy of warfarin anticoagulation over ASA for other types of embolic stroke, anticoagulation is expected to be superior to ASA in ESUS patients. The direct oral Factor Xa-inhibitor rivaroxaban, when compared with VKAs, has been demonstrated to be effective against embolic stroke related to non-valvular AF. Because of its predictable anticoagulant activity and low risk of intracranial hemorrhage, it is expected that rivaroxaban will reduce stroke recurrence in ESUS compared with ASA, and with an acceptable safety (bleeding) profile. Rivaroxaban has also been shown to be efficacious for the treatment of DVT and PE, prevention of recurrent DVT and PE, prevention of VTE following total hip and total knee replacement, and also for prevention of atherothrombotic events after an ACS with elevated cardiac biomarker. Rivaroxaban has no dietary restrictions and only few drug interactions and does not require routine coagulation laboratory monitoring.

Given these considerations, a large, multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study comparing rivaroxaban 15 mg o.d. with

ASA 100 mg o.d. for the secondary prevention of stroke and prevention of systemic embolism will be conducted.

1.7 Dose rationale

This will be the first study investigating rivaroxaban for secondary prevention of stroke in patients with ESUS.

Data in patients with NVAF in the ROCKET-AF study with rivaroxaban as well as data from other new oral anticoagulants (apixaban, dabigatran, edoxaban) and Vitamin K antagonists give support for the benefit of rivaroxaban in this indication, as in both patient populations strokes are primarily of thromboembolic origin. Apixaban, one of the Factor Xa inhibitors showed superiority to ASA (AVERROES study). However, studies comparing anticoagulants to antiplatelets have shown higher bleeding rates.

We assume that in the proposed study rivaroxaban 15 mg will reduce recurrent stroke and systemic embolism as compared to ASA 100 mg. 15 mg is expected to show significant efficacy combined with an acceptable bleeding profile for the following reasons:

- A dose as high as 20 mg as used in embolic stroke prevention in patients with non-valvular atrial fibrillation (ROCKET AF study) might not be necessary for efficacy
 - Modelling data show an overlap of exposure (rivaroxaban plasma concentrations over time) for 15 mg with 20 mg rivaroxaban
 - 15 mg was effective and safe in ROCKET AF in patients with moderate renal impairment and J-ROCKET in patients with normal/mild renal impairment
- 15 mg rivaroxaban will likely lead to less bleeding compared to 20 mg, which is important in an ESUS population that is more vulnerable for intracranial hemorrhage

Because the dose selected for this study is already an adjustment down from the dose used for stroke prophylaxis in NVAF, a dose adjustment for patients with moderate-severe renal impairment is not considered necessary.

1.8 Benefit/risk assessment

Worldwide, 16 million people suffer a first ever stroke annually and 25% of all ischemic strokes are recurrent strokes. The ischemic stroke recurrence rate is substantial and remains at 3 to 6% per year during ASA treatment, the standard guideline recommended antithrombotic therapy for secondary prevention in most patients without major-risk cardioembolic causes.

No specific treatment has been tested for patients with ESUS. Only recently have insights into this disease revealed that most of these strokes are due to embolism. Data from the WARSS study and clinical trials with oral anticoagulants in patients with non-valvular atrial fibrillation support that anticoagulation is likely to be the better treatment option for embolic stroke compared with antiplatelet therapy. Based on these findings, it is expected that the NAVIGATE ESUS trial will show that rivaroxaban is superior to ASA for secondary prevention of stroke in patients with ESUS.

Rivaroxaban has been well tolerated in all studies conducted to date. The main safety finding is bleeding, a recognized complication shared by all anticoagulants. Occurrence of major bleeding is relatively low and importantly, intracranial bleeding was substantially lower in patients receiving rivaroxaban compared to warfarin in the ROCKET-AF study.

The 15 mg o.d. dose for rivaroxaban has been selected to balance benefit and risk for ESUS patients treated in the study.

Approximately 25% of the worldwide stroke incidence is caused by ESUS. If the results of this trial, which will focus on this population of patients, favors the use of rivaroxaban, millions of patients could benefit from this treatment.

2. Study objectives

The primary efficacy objective is:

- To evaluate whether rivaroxaban is superior to aspirin in reducing the risk of recurrent stroke and systemic embolism in patients with a recent ESUS

The secondary efficacy objective is:

- To evaluate whether rivaroxaban is superior to aspirin in reducing the risk of cerebrovascular events, cardiovascular events, and mortality in patients with a recent ESUS

The safety objective is to document the incidence of clinically relevant bleeding.

3. Investigators and other study personnel

3.1 Investigator

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 sheet before patient recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center.

3.2 Study personnel

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

3.3 Study committees

Separate charters will be prepared for all study committees overseeing the study including the personnel, responsibilities, procedures, and meeting frequencies.

3.3.1 Steering Committee

The Steering Committee (SC) will consist of the 2 co-principal investigators, National Leaders from all countries, and sponsor representatives. The SC 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 SC will convene regularly to discuss and report on ongoing supervision of the study.

3.3.2 Independent Data Monitoring Committee

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 and/or cardiovascular disease, and biostatistics; and who are not members of the SC, or involved as investigators or otherwise in the trial.

3.3.3 Independent Central Adjudication Committee

The Independent Central Adjudication Committee (ICAC) will comprise members with clinical and methodological expertise in neurology and cardiology who will be responsible for adjudication and classification of outcome events in the study.

4. Study design

4.1 Overview

This is a multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study in patients with a recent ESUS.

Following provision of informed consent, patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomly allocated by an interactive voice/web response system (IxRS) to either rivaroxaban 15 mg o.d. or ASA 100 mg o.d. in a 1:1 ratio. No dose adjustment will be made for patients with mild or moderate renal impairment.

Patients may be randomized and receive the first study medication intake between 7 days and 6 months after the index stroke event. In case of minor strokes (National Institutes of Health Stroke Score [NIHSS] ≤ 3), study medication may be initiated as early as 3 days after stroke onset if all eligibility assessments have been completed. In the presence of hemorrhagic transformation on the qualifying brain imaging study or if intravenous thrombolysis therapy was given for the index stroke, study medication will not be initiated before 10 days after the acute stroke event unless a repeat CT or magnetic resonance imaging (MRI) performed before randomization documents the absence of new or extension of hemorrhage.

Patients will be enrolled as early as possible after the required diagnostic evaluation is complete and eligibility criteria are fulfilled. The goal is that the majority of patients are enrolled within 3 months, and fewer patients between 3 and 6 months.

Randomization will be stratified by country and age <60 and ≥ 60 years. No more than 10% of the total patient population will be randomized into the age group <60 years, as patients with <60 years have a lower risk for recurrent stroke. Patients < 60 years will need to have at

least one risk factor such as stroke or TIA prior to index stroke, diabetes, hypertension, and heart failure.

At randomization, patients will receive study medication and instructions for its administration. Thereafter, patients will return to the clinic at 1, 6, and 12 months and then every 6 months until the end of study (efficacy cut-off date) is announced. At 3 months, the patient will be contacted by telephone. Throughout the study and at clinic visits, patients will be assessed for efficacy (stroke, systemic embolism, MI, CV death, or all-cause mortality) and safety (vital signs, bleeding, serious adverse events [SAEs] which are not outcome events, non-serious adverse events [AE]s leading to permanent discontinuation of study treatment, and any non-serious AEs of particular concern to the investigator).

The trial will continue until approximately 450 patients are anticipated to have experienced a positively adjudicated primary efficacy outcome event. This is anticipated to occur approximately 3 years after the first patient is randomized, but may vary depending on the recruitment rate as well as the primary event rate. A telephone safety visit will be performed 1 month after the end-of-treatment (EOT) visit.

Patients permanently discontinuing study treatment will continue to be followed, and outcome events and vital status must be assessed in these patients until the end of the study via either clinic visits or telephone contacts.

All efficacy and safety analyses are based on time from randomization to time of first event. Suspected clinical study outcomes will be assessed by the ICAC, which will be blinded to treatment allocation. Adjudicated results will be the basis for the final analyses. The IDMC will monitor patient safety during the study and give recommendations to the SC and sponsor.

A schematic of the study design is provided in [Figure 4–1](#).

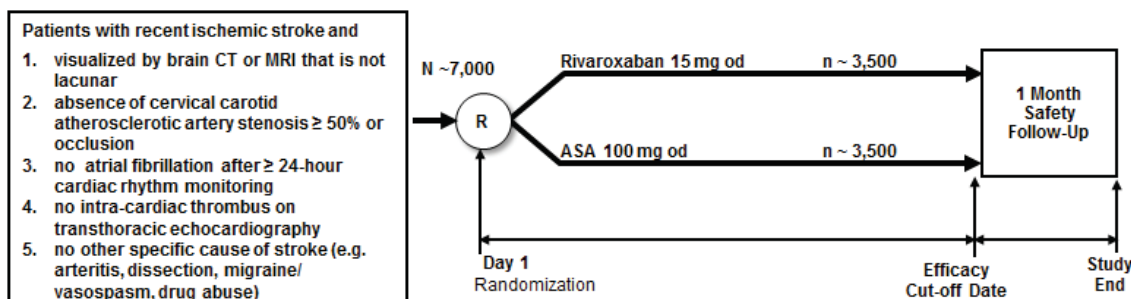


Figure 4–1: Study design schematic

4.2 Justification of the design

The target patient population comprises patients with a recent ESUS. These patients have substantial risk for recurrent stroke and other thromboembolic events despite antiplatelet therapy, the current standard of care. A double-blind, randomized trial design comparing rivaroxaban with ASA is deemed the most appropriate design to allow for an unbiased

evaluation of rivaroxaban as a treatment option for this patient population in an international trial.

4.3 End of study

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 final efficacy outcome event has been adjudicated for patients from all participating clinical sites (EU and non-EU).

5. Study population

This Phase III, multi-national, study will be conducted in 25 to 30 countries worldwide in approximately 7000 patients recruited primarily from hospital-based stroke units. Patients who will be enrolled in this study must meet all of the inclusion criteria and none of the exclusion criteria listed in Section 5.1.

5.1 Eligibility

5.1.1 Inclusion criteria

1. Embolic stroke of undetermined source (ESUS) defined as:
 - Recent ischemic stroke (including TIA with positive neuroimaging) visualized by brain CT or MRI that is not lacunar (i.e., subcortical infarct ≤ 1.5 cm), and
 - Absence of cervical carotid atherosclerotic stenosis (or vertebral and basilar artery stenosis in case of posterior circulation stroke), that is $\geq 50\%$, or occlusion in arteries supplying the area of ischemia in CT or magnetic resonance (MR) angiography or ultrasound, and
 - No history of AF, no documented AF on 12-lead electrocardiogram (ECG) or episode of AF lasting 6 minutes or longer detected after ≥ 24 -hour cardiac rhythm monitoring (Holter or telemetry), and
 - No intra-cardiac thrombus on transthoracic echocardiography, and
 - No other specific cause of stroke identified by routine clinical care (e.g., arteritis, dissection, migraine/vasospasm, drug abuse)
2. Time from recent ischemic stroke to randomization and first study medication intake (and only if the investigator regards it as safe to initiate therapy with an anticoagulant) between 7 days and 6 months except:
 - in case of minor strokes (NIHSS ≤ 3), study medication may be initiated as early as 3 days after stroke onset.
 - in case of intravenous thrombolysis treatment or hemorrhagic transformation seen on the qualifying CT or MRI, study medication will not be initiated before 10 days after

the acute stroke event unless a repeat CT or MRI scan performed before randomization documents the absence of no new or extension of hemorrhage.

3. All planned diagnostic tests for stroke evaluation must be completed. Brain imaging and 24-hour cardiac monitoring must be repeated if new symptoms of stroke/TIA occurred after the initial stroke evaluation, as does 24-hour cardiac monitoring if symptoms suggestive of AF occur.
4. Age ≥ 18 years (or respective country specific legal lower age limit if this is >18 years)
5. For patients with age < 60 years at least one of the following risk factors: stroke or TIA prior to index stroke, diabetes, hypertension, and heart failure
6. Written informed consent consistent with local regulations governing research in human subjects

5.1.2 Exclusion criteria

1. Severely disabling stroke (modified Rankin score ≥ 4 at screening)
2. If imaging of intracranial arteries is performed by CT or MR angiography or transcranial Doppler: $\geq 50\%$ luminal stenosis or occlusion in arteries supplying the area of ischemia
3. Patent foramen ovale with plans for closure
4. Known serious infection or inflammatory disease that may be the cause of stroke
5. Patient has or is intended to receive an implantable ECG loop recorder
6. Indication for chronic anticoagulation based on guideline recommendations or investigator's judgment; e.g., patient with prosthetic mechanical valve, venous thromboembolism, hypercoagulable state
7. Indication for chronic antiplatelet therapy based on investigator's judgment, in which anticoagulation is not a reasonable substitute, or chronic therapy with a conventional non-steroid anti-inflammatory drug (NSAID) for a non-stroke indication
8. Hypersensitivity or any other contraindication listed in the local labeling for ASA or rivaroxaban
9. Active bleeding, major bleeding within last 6 months, history of primary intracranial hemorrhage or high risk for serious bleeding contraindicating anticoagulant or antiplatelet therapy
10. Hepatic disease associated with coagulopathy (prothrombin time prolonged beyond the normal range) and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
11. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² as assessed at local laboratory within 1 month of screening
12. Life expectancy less than 6 months
13. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), i.e., human immunodeficiency virus protease inhibitors and

the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, or posaconazole, if used systemically

14. Female of childbearing potential who are not surgically sterile, or, if sexually active not willing to use adequate contraceptive measures with a failure rate less than 1% per year (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, male partner sterilization) before entry and throughout the study, as well as pregnant or breast feeding women
15. Inability to cooperate with the study procedures
16. Previous randomization to this study or participation in a study with an investigational drug or medical device within 30 days prior to randomization
17. 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)

5.2 Discontinuation of patients from study treatment

An excessive rate of patient discontinuations from either treatment or “drop-outs” from the study may render the trial non-interpretable. In this study, outcome 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 will be taken to motivate patients to comply with all study procedures and to continue to be followed until the end of the trial.**

Patients may discontinue study medication at their own request and without giving reasons (even though providing a reason is encouraged), based on the investigator’s judgment, if the patient is pregnant, or at the request of the sponsor (exceptional circumstances). In case a patient is diagnosed with atrial fibrillation during the study trial medication must be stopped (see section 6.9.2). **Study drug will not be routinely discontinued in participants reaching a potential outcome event unless there is a safety concern or a clear indication for an alternative antithrombotic therapy as determined by the local investigator.**

In case of a temporary study medication discontinuation for any reason, study medication will be restarted as soon as medically justified in the opinion of the investigator. There is no defined maximum limit for temporary treatment interruption.

For all patients who permanently discontinue study medication, the patients will still be part of the study, and outcome events and vital status must be reported until the efficacy cut-off date for the study is announced. All safety data will continue to be collected for 1 month after the last study medication intake (safety follow-up visit). The investigator and patient must discuss and determine further follow-up options. Options for follow-up are listed below, in descending order of preference:

1. Patient continues the regular study clinic visits at the investigator’s site as outlined in the protocol
2. Patient will be contacted by phone at the regular follow-up intervals
3. Patient allows his/her general practitioner or a family relative to be contacted (if allowed in respective country) at the regular follow-up interval

4. Patient will be contacted once at the end of the study
5. Patient withdraws consent. This will be the last option and means that the patient does not agree to any kind of follow-up and specifically refuses any further contact with the investigator. This should happen only in exceptional cases. If possible by local regulations, this decision will be provided in writing. Vital status will be obtained at study end through public information according to local guidelines and as allowed by local regulations.

For patients who do not agree to attend regular study visits, the investigator will encourage the patient to return to the clinic for at least one final visit in order to perform all assessments as outlined for the EOT visit.

If a patient fails to return for a study visit or is lost-to-follow-up, the investigator should explore all possible options to contact the patient. In that respect, the investigator should ask the patient at the study start for the contact details of a relative or friend who can be contacted in case the patient cannot be reached. The site must document all attempts to try to contact the patient in the medical records/source documents. If all attempts fail, depending on local legislation, death registries or other registries may be accessed or private investigation to locate a patient may be initiated.

If study medication is temporarily interrupted or permanently discontinued, the investigator will document the reason for in the medical records and on the electronic case report form (eCRF).

Patients who permanently discontinue the study for any reason will not be reactivated.

5.3 Patient 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 time of randomization. This randomization number will allow subsequent identification of treatment allocation.

6. Treatments

6.1 Treatments to be administered

The treatments to be administered are rivaroxaban 15 mg o.d. or ASA 100 mg o.d..

6.2 Identity of study treatment

All study drugs 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.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance (QA) group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor study file.

6.3 Treatment assignment

Patients will be randomly assigned to treatment in a blinded manner to one of 2 study arms:

- Rivaroxaban plus placebo ASA
- ASA plus placebo rivaroxaban

Allocation to treatment will be done centrally by IxRS. Allocation will be performed in a 1:1 ratio to each study treatment and will be stratified by country and by age (<60 or ≥60 year).

No more than 10% of the total patient number will be randomized into the age group <60 years.

Specific procedures for treatment assignment through the IxRS are described in the IxRS manual.

6.4 Dosage and administration

Patients will be provided with a high-density polyethylene (HDPE) -bottle containing immediate-release film-coated tablets of rivaroxaban 15 mg or matching placebo and an HDPE bottle containing enteric-coated tablets of ASA 100 mg or matching placebo.

One tablet from each bottle should be taken once daily with food. If a dose is missed the patient should take study medication immediately and continue on the following day with the once daily intake. The dose should not be doubled within the same day to make up for a missed dose.

6.5 Blinding

The study is double-blinded using matching placebo medication as described in Section 6.4.

6.5.1 Emergency unblinding by the investigator

Unnecessary unblinding should be avoided and should only be undertaken by the investigator when it is essential for the patient's safety. In such a situation, the investigator will be able to unblind the patient via the IxRS system.

Investigators will be provided with the details on the emergency unblinding procedure at study start.

For unblinding in case of a Suspected Unexpected Serious Adverse Reaction (SUSAR) see Section 7.5.3.2.

6.6 Drug logistics and accountability

Study medication will be provided by Bayer and labeled according to local law and regulation. A complete record of batch numbers, expiry dates and labels will be maintained in the study file.

All study medication needs 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 should not be stored above 30°C. The study drug is to be kept in a secure area (e.g., locked cabinet) without access to unauthorized personnel. Site personnel will confirm receipt of study medication via IxRS and will use study medication only for this study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study medication must be properly documented according to local regulation and specified procedures.

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

6.7 Treatment compliance

Compliance will be evaluated by interview and by counting the tablets returned by the patient to the site versus the tablets expected to be taken by the patient.

First dose, last dose, and any dose interruptions of study medication due to AEs or of >7 days for any other reason will be reported in the eCRF.

6.8 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.

6.9 Prior and concomitant therapy

Acute and chronic therapies given for the qualifying stroke will be recorded in the eCRF. During the study, chronic concomitant therapy will be recorded at the visits (cerebro- and cardiovascular therapies) or at the time of occurrence of any efficacy outcome, bleeding, or SAE.

For patients at risk of 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 by the study.

6.9.1 Guidance for management of participants who require antiplatelet therapy or non-steroidal anti-inflammatory drug during the study

Patients who enter the study receiving antiplatelet therapy (e.g., ASA) will have non-study antiplatelet therapy discontinued when study medication is started.

The concomitant use of NSAID and non-study antiplatelet therapy during the study is strongly discouraged since it increases the risk for bleeding. However, if a NSAID drug is indicated, the lowest possible dosage must be selected. Should analgesics be needed, use of paracetamol/acetaminophen is recommended.

6.9.2 Guidance for management of participants who have atrial fibrillation identified during study

If a patient is diagnosed with AF during the study that requires oral anticoagulation according to the investigator's judgment, the patient will stop double-blind study medication. Per protocol, study medication must be permanently discontinued if an AF episode of > 6 minutes is identified. The patient will be offered open-label rivaroxaban according to the local label (if acceptable by local regulations) or alternatively, the investigator may prescribe other standard of care e.g., VKA. If the patient is switched to a VKA, adequate anticoagulation during the initiation phase needs to be ensured according to the Xarelto® summary of product characteristics, due to the length of time required to achieve therapeutic anticoagulation with VKAs.

Patients receiving open-label rivaroxaban will continue with the regular study visits. For patients treated differently, the instructions for permanent discontinuation of study medication as outlined in Section 5.2 should be followed.

6.9.3 Guidance for management of participants who have coronary artery disease identified during the study

Patients diagnosed with coronary artery disease (CAD) during the study and in whom treatment with dual antiplatelet therapy is warranted (e.g., after percutaneous coronary intervention [PCI]) will interrupt study medication for the duration of dual antiplatelet therapy, as the combination of dual antiplatelet therapy and rivaroxaban 15 mg may lead to an increased bleeding risk. Study medication will be restarted once dual antiplatelet therapy is stopped.

For patients in whom treatment with ASA is recommended (e.g., stable CAD) the investigator can consider continuing study medication with non-study ASA only if the dose of ASA is ≤100 mg daily. Use of higher doses of ASA will require interruption of study medication.

6.9.4 Guidance for management of participants who have a recurrent ischemic stroke during the study

For patients who have a recurrent ischemic stroke during the study, a complete diagnostic work-up including brain imaging, at least 24-hour cardiac rhythm monitoring, and echocardiography is encouraged. All available clinically-obtained diagnostic results will be recorded on eCRFs for the purposes of event adjudication and secondary analyses.

No high-quality data are available regarding the use of intravenous thrombolysis for acute stroke in patients receiving rivaroxaban; therefore, the use of thrombolytic agents will follow local practice.

Based on the half-life of rivaroxaban of 11-13 hours in elderly patients, it may be anticipated that little or no drug is present in circulation, if the last dose of study medication was given at least 48 hours before. The anti-Factor Xa chromogenic assay, when used with validated calibrators and controls and where available, may be used to confirm that little or no residual anticoagulant effect is present. In addition, a normal prothrombin time (PT) value (measured

using a rivaroxaban-sensitive reagent) suggests there is no clinically relevant anticoagulant effect of rivaroxaban.

As there is no contraindication for use of intravenous thrombolysis in patients with acute ischemic stroke who are receiving ASA, the treatment assignment can be emergently unblinded to facilitate decisions regarding intravenous thrombolysis.

Mechanical clot removal may be performed in any case.

6.9.5 Guidance for management of participants who have bleeding during the study

If a patient has serious bleeding during study treatment, the following routine measures could be considered:

- Delay the next study medication administration or discontinue study medication, if indicated
- Consider usual supportive treatment for bleeding, including local control of bleeding (if possible), fluid replacement, and blood transfusion

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

- Prothrombin complex concentrate (PCC)
- Activated prothrombin complex concentrate (APCC)
- Recombinant Factor VIIa

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Due to the high plasma protein binding, rivaroxaban is not expected to be dialysable.

6.9.6 Guidance for management of participants with overdose

Due to limited absorption, a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific antidote is not available. The use of activated charcoal to reduce absorption may be considered.

7. Procedures and variables

7.1 Schedule of procedures

As this is an event-driven study, patients will have different numbers of study visits. Patients will visit the clinic at screening, randomization, 1, 6, and 12 months and then every 6 months until the end of the study. At 3 months after randomization, the patient will be contacted by telephone. Patients will come to the clinic for an EOT visit followed by a telephone contact (Safety Visit) 1 month later.

7.1.1 Tabulated overview

A tabulated overview of the procedures conducted in this study is provided in the Table of procedures, provided at the end of the Synopsis.

7.1.2 Timing of assessments

7.1.2.1 Visit 1 (Screening)

Visit 1 will be used to assess the eligibility of the patient. After obtaining signed informed consent, the investigator will review the diagnostic tests required to diagnose ESUS. All diagnostic assessments for ESUS must be completed before the screening visit. All acute therapies for stroke (e.g., thrombolysis) and diagnostic tests performed to diagnose acute stroke and ESUS will be recorded in the eCRF.

Demographic data (age, gender, race/ethnicity), weight (kg), height (cm), and medical history including reporting of stroke risk factors will be recorded at this visit. Laboratory assessments will include creatinine and eGFR (if not conducted at local laboratory within 1 month before screening, use value for eGFR as reported on laboratory report, otherwise calculate eGFR using MDRD formula, for which a calculator can be found for example on the internet www.mdrd.com) and pregnancy testing (only in women of childbearing potential). The modified Rankin score will be assessed as part of the exclusion criteria and NIHSS as part of the inclusion criteria.

7.1.2.2 Visit 2 (Randomization Visit)

Once all inclusion/exclusion criteria are fulfilled the patient will be randomized by accessing the IxRS system. The study medication will be assigned, and the patient will receive the study medication and instructions for its administration. The first dose of study medication can be given at this visit or at the time the patient will usually take study medication (same day or next day).

During this visit, study procedures will include the recording of ConMeds (Section 6.9) and vital signs (blood pressure [millimeters of mercury; mmHg] and heart rate [beats per minute; bpm]). Outcomes research questionnaires (Section 7.6.1) will be completed by the patient:

- European Quality of Life-5 Dimensions (EQ-5D) Questionnaire
- Montreal Cognitive Assessment (MoCA)
- Digit Symbol Substitution (DSS) test
- Standard Assessment of Global-Activities in the Elderly (SAGE) questionnaire

Procedures for Visits 1 and 2 may be combined and performed at the same visit, if all eligibility criteria can be assessed at Visit 1 and no additional assessments are required before randomization (e.g., eGFR).

7.1.2.3 Regular study visits (Visits 3 and onward)

Patients will return to the study clinic at 1 month, 6 months, and then every 6 months. At 3 months, the patient will receive a telephone call to obtain safety and outcome data and reinforce adherence to study medication and to avoiding non-study ASA.

The patient will be instructed to report any hospitalization or other significant illness to the investigator on an ongoing basis in order to allow a timely reporting of study outcomes and SAEs. In addition, at all visits, the patient will be specifically asked about potential study outcomes and AEs. If a suspected study outcome is reported, the respective eCRF will be completed and an adjudication package expeditiously compiled and submitted.

Vital signs will be collected at 6 months, 1 year, and then yearly thereafter.

Concomitant medications and weight will be collected once per year. If an SAE is reported, the use of any additional ConMeds should be recorded at that time.

The outcomes research questionnaires (MoCA, DSS, and SAGE) will be completed by the patient at the 1 year visit only. The EQ-5D will be completed every 6 months.

If a recurrent stroke is reported, the modified Rankin Score is to be assessed at 7 days post stroke or at hospital discharge, if this occurs before 7 days, and again at 3 months post stroke. The modified Rankin score is also to be recorded at 1 year after stroke.

Study medication will be dispensed and returned every 6 months and study drug accountability and compliance will be recorded at these visits.

7.1.2.4 End of treatment (EOT) visit

When the sponsor announces the end of the study (efficacy cut-off date), all patients must return to the clinic within 6 weeks in order to make a final assessment. At this visit, study procedures will include the collection of efficacy and safety outcome data, (S)AEs, vital signs, ConMeds, EQ-5D, MoCA, DSS and SAGE questionnaires, and modified Rankin score. In addition, the study staff will collect the patient's empty and unused study medication bottles to allow final drug accountability and compliance checks.

Study medication 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.

7.1.2.5 Safety visit

Patients will be contacted by **telephone** 1 month after the last study medication intake to allow the collection of safety data.

7.2 Population characteristics

7.2.1 Demographics

Demographics include age, gender, race/ethnicity

7.2.2 Medical history

Medical history findings (i.e., previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the informed consent form (ICF)
- Considered relevant to the study

Medical history parameters to be collected at screening will include:

- Disease history associated with cerebro- and cardiovascular diseases and risk factors (stroke, transient ischemic attack, MI, angina pectoris, heart failure, peripheral artery disease, diabetes, hypertension, tobacco use)
- Surgical history (cerebro- and cardiovascular revascularizations)
- Other relevant diseases (renal dysfunction, liver disease, cancer, bleeding requiring transfusion)

7.3 Efficacy

7.3.1 Assessments and procedures at occurrence of efficacy outcome events

The analysis of efficacy outcome events will be based on events as adjudicated by the ICAC.

Occurrence of outcomes must be reported within 3 days of the site's notification of the event. Patients are requested to inform the site as soon as possible if they are hospitalized (regardless of reason) in order to ensure timely identification of potential CV events.

The following events will be reported on Outcome/CV Event reporting forms and will undergo adjudication by the ICAC:

- All deaths
- Stroke (ischemic, hemorrhagic or undetermined) and TIA
- Systemic embolism
- MI and hospitalization for cardiac chest pain

These events are exempted from SAE reporting with the exception of non-CV deaths.

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

7.3.2 Definition of efficacy outcome events

The following efficacy outcome events will be assessed and are defined in the following subsections of this protocol:

- stroke (Section 7.3.2.1)
- systemic embolism (Section 7.3.2.2)
- MI (Section 7.3.2.3)
- CV death (Section 7.3.2.4)
- all-cause mortality (Section 7.3.2.5)

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

7.3.2.1 Stroke

Stroke is 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 <24 hours, stroke requires neuroimaging evidence of acute brain ischemia (i.e. TIA with positive neuroimaging).

7.3.2.2 Systemic embolism

Systemic embolism is defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms.

7.3.2.3 Myocardial infarction

The term acute MI is used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. The diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The MI Universal Definition from 2012 (28) describes 5 types of myocardial infarction:

- Type 1 Spontaneous myocardial infarction
- Type 2 MI secondary to an ischemic imbalance
- Type 3 MI resulting in death when biomarker values are unavailable
- Type 4a MI related to percutaneous coronary intervention (PCI)
- Type 4b MI related to stent thrombosis
- Type 5 MI related to coronary artery bypass grafting (CABG)

7.3.2.4 Cardiovascular death

Cardiovascular death includes death due to stroke, myocardial infarction, heart failure or cardiogenic shock, sudden death or any other death due to other cardiovascular causes. In addition, death due to hemorrhage will be included.

7.3.2.5 All-cause mortality

All-cause mortality includes all deaths.

7.3.3 Efficacy variables

7.3.3.1 Primary efficacy variable

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

- Stroke (ischemic, hemorrhagic, and undefined stroke, TIA with positive neuroimaging)
- Systemic embolism

7.3.3.2 Secondary efficacy variables

The secondary efficacy variables of this study are the time from randomization to first occurrence of:

- Cardiovascular death (including death due to hemorrhage), recurrent stroke, systemic embolism, and MI
- All-cause mortality
- Individual components of the primary and secondary efficacy outcomes (stroke, CV death, and MI) as well as ischemic stroke, and disabling stroke (modified Rankin score 4 and 5)

7.4 Pharmacokinetics/pharmacodynamics

Not applicable.

7.5 Safety

The safety outcomes are bleeding events using the International Society on Thrombosis and Haemostasis (ISTH) major bleeding definition (29), and other definitions derived from these as listed in Section 7.5.1 and Section 7.5.2. Bleeding events will be reported on the bleeding reporting forms and exempted from SAE reporting. Potential major bleeding will undergo adjudication.

Information on bleeding will be collected in a way to also allow additional analysis using different bleeding definitions, e.g., Thrombolysis In Myocardial Infarction (TIMI) major bleeding and Global Use of Strategies to Open Occluded Arteries (GUSTO)

severe/life-threatening bleeding. The analysis will be defined in the statistical analysis plan (SAP).

7.5.1 Primary safety variable

The primary safety variable is the time from randomization to time of first occurrence of a major bleeding defined as a bleeding event that meets at least one of the following criteria:

- Fatal bleeding, and/or
- Bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), and/or
- Clinically overt bleeding associated with a recent decrease in the hemoglobin level of more than 2 g/dL (20 g/L; 1.24 mmol/L) compared to the most recent hemoglobin value available before the event, and/or
- Clinically overt bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood

7.5.2 Secondary safety variables

The secondary safety variables are the time from randomization to time of first occurrence of:

- Life-threatening bleeding, defined as a subset of major bleeding that meet at least one of the following criteria:
 - Fatal bleeding
 - Symptomatic intracranial bleeding
 - Reduction in hemoglobin of at least 5 g/dl (50 g/l; 3.10 mmol/L)
 - Transfusion of at least 4 units of packed red cells or whole blood
 - Associated with hypotension requiring the use of intravenous inotropic agents
 - Necessitated surgical intervention
- Clinically relevant non-major bleeding, defined as non-major overt bleeding but
 - Requires medical attention (e.g., hospitalization, medical treatment for bleeding), and/or
 - Is associated with a study drug interruption of more than 14 days.
- Intracranial hemorrhage

7.5.3 Adverse events

7.5.3.1 Definitions

An **adverse event** (AE) is any untoward medical occurrence including an exacerbation of a pre-existing condition or abnormal laboratory finding in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE is considered serious (SAE) if it fulfills one or more of the following criteria:

- Results in death
- Is life-threatening
- Requires or prolongs hospitalization
- Is a congenital anomaly or birth defect
- Is a persistent or significant disability/incapacity
- Is another important medical event

Important medical event: Any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Important medical events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

Hospitalizations, which were planned before inclusion in the study (e.g., elective or scheduled surgery or other interventions arranged prior to the start of the study), will not be regarded as SAEs. This pertains also to hospitalizations which are ambulant (<12 hours) or are part of the normal treatment or monitoring of the studied disease or another disease present before inclusion in the study and which are not due to a worsening of the disease.

When AEs are captured on the Adverse Event Report Form of the eCRF its seriousness, duration, relationship to study drug, action taken, and outcome must be addressed.

7.5.3.2 Adverse event reporting

The safety observation period extends from the time the signed informed consent is obtained through the completion of the final study visit, 1 month post the EOT visit. In case of permanent discontinuation of study medication, AEs other than outcome events must be reported up to 1 month after the last dose of study medication intake (Safety Visit).

All SAEs, all non-serious AEs leading to permanent discontinuation of study-drug treatment, and any non-serious AEs of particular concern to the investigator will be captured in the eCRF. Other non-serious AEs will not be collected due to the large available safety database for rivaroxaban.

The following detailed rules apply to AE and SAE handling:

- SAEs which are primary or secondary efficacy outcomes or appear indicative of an outcome event, e.g., TIA, MI or cardiac chest pain requiring hospitalization will be captured on an Outcome/CV Event page of the eCRF.
- All fatal events which are not considered cardiovascular deaths will be captured as outcomes (Death eCRF) but will also be reported to the sponsor's Pharmacovigilance (PV) Department in an expedited manner.
- All bleeding events including fatal bleeding will be captured in the eCRF (Bleeding page). Serious adverse events which are bleeding terms will not be reported to the sponsor's PV Department in an expedited manner.

- All other events (including complications of efficacy or safety outcome events) that fulfill the seriousness criteria will be reported as SAEs in an expedited manner.
- All pregnancies in female study patients or in female partners of a male study patient will be reported as Pregnancy reports in an expedited manner.
- Non-serious AEs that have led to permanent study-drug discontinuation will be recorded on the AE page of the eCRF.
- Non-serious AEs which the investigator considers of particular concern will be recorded on the AE page of the eCRF. These may include events that are unexpected and/or reveal a pattern that is suggestive of a possible causal association or other non-serious events significant enough as to prompt the investigator to bring them to the attention of the sponsor.
- Out of the AEs reported to sponsor's PV Department, reportable events (i.e., SUSARs) will be unblinded and reported to the competent authorities and Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) according to legal requirements.
- In order to maintain the integrity of the study, SUSARs that derive from outcome events including complications of outcome events (e.g., those arising from lack of expected drug effect or from hemorrhagic events, whether or not fatal) will be exempted from unblinding during the course of the trial and from expedited reporting as SUSARs. However, cases including non CV deaths will be eligible for unblinding and SUSAR reporting.

If reported, SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

A schematic of the outcome and event collection and reporting process is provided in [Figure 7-1](#).

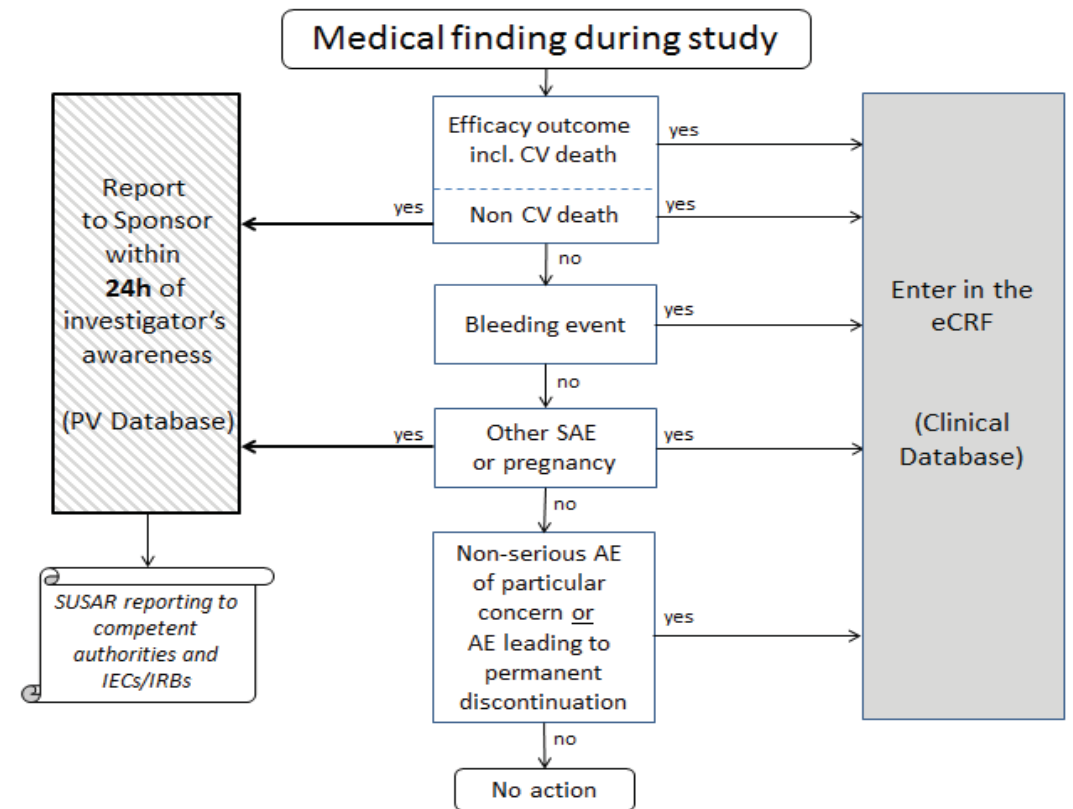


Figure 7-1: Outcome and adverse-event collection and reporting schematic

The investigator must report immediately (within 24 hours of the investigator’s awareness) all SAEs described above as requiring expedited reporting to sponsor’s PV Department. The report recipients are detailed in the instructions for SAE reporting included in the Investigator File.

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.

7.5.3.3 Causal relationship of adverse events to study drug

The assessment of the causal relationship between an AE and the use of study drug is a clinical decision made by the investigator, who is a qualified physician, based on all available information at the time of the completion of the eCRF. The assessment is based on the question whether or not there was a "reasonable possibility" that the study drug caused the event. Possible answers are “yes” or “no”.

An assessment of *no* would include the existence of a clear alternative explanation. Other reason for an assessment of *no* may be lack of 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 developing a few days after the first drug administration.

An assessment of *yes* indicates that there is a reasonable suspicion that the AE is associated with the use of the study drug. Factors in assessing the relationship of the AE to study drug include the temporal sequence from drug administration (the event should occur after the drug is given) and the length of time from drug exposure to event should be evaluated in the clinical context of the event. Furthermore, recovery on drug discontinuation (de-challenge), and recurrence on drug re-introduction (re-challenge, if available), underlying, concomitant, or intercurrent diseases should be evaluated in the context of the natural history and course of the disease being treated. In addition, concomitant medication or treatment, the pharmacology and pharmacokinetics of study drug should be considered.

7.5.3.4 Intensity of an adverse event, action taken, and outcome

The intensity of an AE is assessed as mild (usually transient in nature and generally not interfering with normal activities), moderate (sufficiently discomforting to interfere with normal activities), and severe (prevents normal activities).

Any action on study treatment to resolve the AE is to be documented as: study drug withdrawn, interrupted, dose reduced, dose not changed, dose increased, not applicable, or unknown. Other specific treatment of AEs will be documented as: none, remedial drug therapy or other. The outcome of the AE is to be documented as: recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal or unknown.

7.5.3.5 Pregnancy reports

For a study patient, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported. For the pregnancy of a partner of a male study patient, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent. For all pregnancy reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE, i.e., within 24 hours of his/her awareness.

7.5.3.6 Expected adverse events

The expectedness of AEs will be determined by the sponsor according to the applicable reference document which for this study is the most current version of the investigator's brochure (IB)/company core data sheet. If new relevant safety information is identified, it will be integrated into an update of the IB and distributed.

Unexpected adverse events

An unexpected AE is any AE whose specificity or severity is not consistent with the IB or company core data sheet. Also, reports which add significant information on specificity or severity of an already documented AE constitute unexpected AEs. For example, an event

more specific or more severe than described in the investigator brochure would be considered “unexpected”.

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. For handling different events classified as SUSARs see Section 7.5.3.2.

7.6 Other procedures and variables

7.6.1 Health Economics and Outcomes Research

Patients will be asked to complete a quality of life questionnaire, and 3 cognitive and functional assessment questionnaires during the study conduct.

7.6.1.1 Healthcare Resource Use

Health care resource utilization data related to all efficacy and safety outcomes events will be collected for all patients during the study. These will include: hospitalizations (total days length of stay, intensive care unit/cardiac care unit days, ward type); emergency room visits; unscheduled outpatient physician consultations; or visits related to bleeding, surgeries, other selected procedures (inpatient and outpatient); and post-stroke care (status of care, home health or rehabilitation center or long term care). Days off-work will also be documented. Only occurrence of these events (with identifying information such as types of procedures) will be collected. Country-specific cost data will be linked at a later stage.

7.6.1.2 European Quality of Life-5 Dimensions

A quality of life assessment tool, the European Quality of Life-5 Dimensions Questionnaire (EQ-5D) will be administered at Day 0 (randomization), every 6 months, and at the EOT visits. This is a standardized instrument for use as a measure of health outcomes. The assessment is 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.

7.6.1.3 Montreal Cognitive Assessment, Digit Symbol Substitution test, and Standard Assessment of Global-Activities in the Elderly

The MoCA and DSS will be included in the study to assess cognition and the SAGE questionnaire will be used to assess functional outcome. These tests and questionnaires will be administered at Day 0 (randomization), 1 year, and at the EOT visits. The patient will be asked to independently complete the MoCA and DSS tests to the best of their ability. Otherwise, the reason for not completing must be documented. The SAGE questionnaire may be completed with the help of the study staff.

7.6.1.4 Modified Rankin Score

In addition to the regular assessments at screening, 1 year, and EOT, the Modified Rankin Score will be assessed by the investigator at 7 days or at discharge, if this occurs before

7 days, and again at 3 months after a recurrent stroke. The scale spans 0-6, perfect health without symptoms to death.

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 - Dead.

8. Statistical methods and determination of sample size

8.1 General considerations

A general description of the statistical methods is outlined below. An SAP will be provided in a separate document and will contain a more technical and detailed description of the principal features of the planned analyses, e.g., censoring schemes for time-to-event variables.

The core SAP will be finalized prior to study enrollment. Amendments and/or appendices to the core SAP will provide more details on the coding guidelines, data-handling, and output tables and figures. These SAP associated documents are targeted for completion 6 months before planned study end to take into account emerging data external to the trial that could influence study interpretation. All SAP associated documents will be finalized without knowledge of any emerging results from the trial.

Analyses will be performed using SAS software (SAS Institute Inc., Cary, NC, USA).

8.2 Analysis sets

8.2.1 Efficacy data set

The efficacy analysis will be based on the ITT population, which comprises all randomized patients. In the International Conference on Harmonisation (ICH) E9 guideline this is also termed the full analysis set, FAS. Patients will be categorized to the group to which they were assigned by the IxRS.

8.2.2 Safety data set

The safety analysis will be based upon the safety data set (SAF) which will comprise 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.

8.2.3 Data scopes

The following data scopes will be defined for efficacy and safety analyses.

Data scope according to intention-to-treat principle

The ITT data scope includes 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. This will be the primary data scope for the efficacy analyses.

Data scope according to treatment

The on-treatment data scope will include all outcome events observed from randomization until 2 days following permanent discontinuation of the study drug.

8.3 Variables

The efficacy variables are defined in Sections [7.3.3.1](#) and [7.3.3.2](#).

The safety variables are defined in Sections: [7.5.1](#) and [7.5.2](#).

8.3.1 Subgroup variables

The following subgroup analyses based on baseline demographics are planned:

- Age: <60; 60-75; >75 age
- Sex: male; female
- Race: White; Black; Asian; other
- Region: North America; South America; Western Europe; Eastern Europe; Asia
- BMI: < 25; ≥ 25 to < 30; ≥ 30 kg/m²
- Weight: <70; 70-90; >90 kg
- eGFR: <50; 50-80; >80 mL/min
- Stroke or TIA prior to index event: yes or no
- Time from index stroke to randomization: ≤ 30 days; 30 days to 3 months; > 3 months
- Presence of patent foramen ovale: present or absent / not known
- Cardiac rhythm monitoring: <48; ≥ 48 hours
- Hypertension: yes or no
- Diabetes: yes or no

Even though rivaroxaban has not been tested in patients with ESUS, based on earlier studies with rivaroxaban a consistent (relative) treatment effect across all of the planned subgroups is expected. However, higher efficacy event rates are expected for the following subgroups:

older age, females, renal impairment, stroke or TIA prior to index event, hypertension, and diabetes.

8.4 Statistical and analytical plans

Summaries by treatment group using appropriate descriptive statistics will be provided for all study variables including demographic and baseline characteristics. Mean, median, standard deviation, minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables.

8.4.1 Analysis of the primary efficacy variable

In order to evaluate whether rivaroxaban is superior to ASA in prolonging the time to a primary efficacy outcome event in patients with ESUS, the following null hypothesis (H) will be tested at the significance level of 0.025:

$H_{0, PE}: S_R(t) = S_A(t)$ for all time points $t \geq 0$, (i.e. “there is no difference between the rivaroxaban treatment group and the ASA control group regarding the primary efficacy outcome for all time points”)

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 and S_A denotes the survival function of the ASA group.

The following decision rule to test the null hypothesis will be applied:

According to the size of this study, it is justified to assume under $H_{0, PE}$ a sufficiently close approximation of the one-sided stratified (according to age) log-rank test to the normal distribution. If the z-value from the one-sided log-rank test (for the difference $S_R(t) - S_A(t)$ without stratification) is larger than the critical quantile from the normal distribution ($z_{0.975} = 1.96$), the null hypothesis will be rejected in favor of the alternative hypothesis.

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.

Hazard ratio, relative risk reduction, and corresponding two-sided 95% confidence intervals will be estimated based on an age-group stratified Cox proportional hazards models. 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. Censoring will be assumed independent of the treatment group assignment.

Further details will be specified in SAP.

8.4.2 Analysis of secondary efficacy variables

The secondary efficacy outcomes will be ordered and tested in a sequential manner as listed in Section 7.3.3.2

If the superiority of rivaroxaban for the primary outcome is declared, the following alternative hypotheses, superiority of rivaroxaban compared with ASA for the secondary efficacy outcomes will be tested in the sequential order. That is, the subsequent ordered secondary outcome will be tested only if superiority can be shown for the previous outcomes. If an individual test during any step is not statistically significant, further testing may continue but significance will not be claimed. This hierarchical testing procedure will control the global Type 1 error level.

The analysis methods will be similar to those described for the primary efficacy outcome.

8.4.3 Analysis of safety variables

The analysis methods will be similar to those described for the primary efficacy outcome.

8.4.4 Subgroup analysis

Subgroup analyses for the primary efficacy and safety outcomes will be performed based on the same analysis sets and data scopes as in the main analyses of the study outcomes. The subgroup analyses will be presented descriptively without formal hypotheses testing.

Homogeneity of treatment effect in subgroups, both in magnitude and direction, will be assessed by adding a covariate for the subgroup variable and the corresponding treatment-subgroup interaction to the respective Cox proportional hazards model used in the main analysis. Additionally the hazard ratio for the treatment effect will be estimated separately within each level of a subgroup variable using the same Cox proportional hazards. As the number of subgroup analyses may be large, the probability of observing at least one spurious interaction is high despite the lack of a biological or pharmacological basis for expecting an interaction. Thus, any interactions with a p-value below the 5% type I error level in the analysis of primary outcomes will be interpreted as “flags” to prompt further investigation. This further investigation includes the likelihood ratio test proposed by Gail and Simon to test for qualitative interaction.

8.4.5 Handling of missing data

All efforts will be made to collect complete data for all patients randomized in this study. 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 known, the site investigator will be asked to provide a best estimate as to when the event occurred. Even though the exact date of an event is unknown, the investigator often does know some information that would indicate the approximate date, such as the first week of a month, in the fall of a year, or the middle of a particular year, or at least the date when the patient was last seen or contacted. This information can be meaningfully incorporated into the estimated date recorded, as this is likely to be closer to the true date than any produced by an uninformed computer program. This estimated date should

be the middle date within the period that the event is known to have occurred. If the event is known to have occurred in the first week of a month, then the date in the middle of that week should be recorded as the estimate. If it occurred in the fall of a year, then the middle date in the fall is the appropriate estimate. If no information is known then the date in the middle of the plausible time period should be given, based on the last contact with the patient prior to the event and the date of contact when information about the event was known.

8.5 Planned interim analyses

The IDMC will monitor the study for greater than expected efficacy and for safety. There will be 1 formal interim analysis to assess efficacy, which will occur when approximately 67% of the planned primary efficacy events have accrued. The study may be stopped early, if there is overwhelming superiority of rivaroxaban ($p < 0.0001$) for efficacy (e.g., following the conservative Haybittle-Peto approach). 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 over ASA.

The execution of the interim analyses and decision rules will be specified in the IDMC charter and the SAP for the interim analysis.

8.6 Determination of sample size

The study is event-driven and it is estimated that 7000 patients (3500 per treatment group) need to be randomized in order to have approximately 450 patients experiencing a confirmed primary efficacy outcome event. This number of events will allow the demonstration of superiority of rivaroxaban compared to ASA with regard to the primary outcome with a power of 90% and a one-sided level of significance $\alpha = 0.025$ under the following assumptions:

- An average yearly event rate of the composite primary efficacy outcome of 3.8% in the ASA group (4.0% for patients with age ≥ 60 years, 2.0% for 10% of patients with age < 60 years)
- A 30% RRR for stroke and systemic embolism in the rivaroxaban group compared to ASA
- Approximately 10% of patients will permanently discontinue study medication in the first year and 7% in following years
- Approximately 5% of patients with a diagnosis of AF will switch to standard treatment during study conduct
- Approximately 3% patient deaths per year and 1% of patients lost to follow-up per year

Under these assumptions the expected RRR to be observed in this study would be 26% for the primary efficacy outcome.

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

9. Data handling and quality assurance

9.1 Data recording

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the site. The site must implement processes to ensure this happens. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

Data recorded from “only screened patients (screening failures)”

Data of 'only screened patients' will be recorded at least as source data, as far as the reason for the premature discontinuation (reason for not randomizing the patient into the study) is identifiable. At minimum, data to be recorded in the eCRF are demographic information (patient number, date of birth/age, sex, race and ethnicity), the reason for premature discontinuation and date of last visit. These data will be transferred to the respective database.

For screening failures with an SAE, the following additional data should be collected in the eCRF, in addition to demographic information, primary reason for discontinuation and date of last visit:

- All information about the SAE
- All information related to the SAE such as:
 - concomitant medications
 - medical history
 - other information needed for SAE complementary page

9.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's (contract research organization'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.

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.

9.3 Data processing

The data collection tool for this study will be a validated electronic system called iDataFax. Patient data necessary for analysis and reporting will be transmitted into a validated database or data system (e.g., TOSCA; SAS). Clinical data management will be performed in accordance with agreed standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g., IxRS, adjudication committees).

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

9.4 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.

9.5 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.

10. Premature termination of the study

The sponsor has the right to close this study or centers at any time, which may be due but not limited to the following reason:

- If risk-benefit ratio becomes unacceptable owing to, for example,

- Safety findings from this study (e.g., SAEs)
- Results of the review by the IDMC
- Results of parallel clinical studies

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.

Closures should occur only after consultation between involved parties and all affected institutions must be informed as applicable according to local law.

Details for individual patient's discontinuation of study medication and withdrawal of consent can be found in Section 5.2.

11. Ethical and legal aspects

11.1 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 GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IECs/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 IEC/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 10.

11.2 Subject information and consent

All relevant information on the study will be summarized in integrated patient information sheets and ICFs, provided by the sponsor. Sample patient information sheets and ICFs are provided as a document separate to this protocol.

Based on the patient information sheet for the respective study phase, the investigator or designee will explain all relevant aspects of the study to each patient/legal representative or proxy consentor (if the patient is under legal protection), 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 IEC/IRB has been obtained.

Each patient/legal representative or proxy consentor will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the patient/legal representative or proxy consentor voluntarily agrees to sign the ICF and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The patient/legal representative or proxy consentor 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/legal representatives or proxy consentors 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/legal representative or proxy consentor 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.

11.3 Publication policy

The study results will be reported irrespective of the outcome of the study. The SC will decide on the authorship of all papers. The main study results will be written by a writing group lead by members of the SC on behalf of the whole study group, and may include additional individuals who have made substantial and sustained contributions.

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

11.4 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.

11.5 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 or documents sent for adjudication of outcome events), 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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13. Protocol amendments

Not applicable

14. Appendices

14.1 Substudies

Two substudies are planned at selected sites. Participation in the substudies is not a requirement. The substudies do not necessarily need to be conducted at the same sites and in the same patients.

Conduct of these substudies is contingent on review and approval by the appropriate Health Authorities and the site's IRB or EC. Patients must sign separate ICFs for participation in these substudies.

14.1.1 MRI substudy

Covert ischemic strokes are defined as strokes not identified clinically at the time of their occurrence but resulting in radiologic evidence of brain infarction. Covert strokes are frequent with a prevalence of 20% at the age of 65 years and are 5 times as common as symptomatic strokes.^(30,31) Covert strokes may be manifested as subtle cognitive decline, loss of independence, gait impairment, and falls. The post stroke population is characterized as having a high incidence of these covert infarctions (4% to 24% from 3 cohort studies) and subsequent cognitive and functional impairment.⁽³²⁻³⁴⁾

The primary objective of this substudy is to determine the effect of rivaroxaban compared with aspirin on MRI-defined covert infarcts in individuals with a recent ESUS. The primary

analysis will be performed on an ITT population (i.e. all patients with baseline and follow-up MRIs, including those with early study drug discontinuation), based on the assessment by an MRI Core facility. An additional analysis will be performed on patients with baseline and follow-up MRIs who take study drug until the efficacy cutoff date.

Secondary objectives will be to determine the effect of rivaroxaban compared to aspirin for reducing covert and clinical infarcts (i.e. all incident infarcts), the progression of volume of white matter hyperintensities (WMH), functional decline (SAGE), and cognitive decline (DSS, MoCA) in the patients with recent ESUS enrolled in this substudy.

Exploratory objectives will be to determine the imaging profile which predicts clinical recurrence as well as the radiologic pattern of recurrent lesions, and to evaluate the predictors of covert infarcts at baseline in the ESUS population.

Approximately 1000 patients will be enrolled in this substudy that is designed to detect a 35% reduction in covert strokes by rivaroxaban with 80% power and a two-sided alpha of 0.05, assuming an annual covert stroke rate of 10% in patients receiving aspirin, a mean follow-up of 24 months, and a drop-out rate of 15%.

The substudy will be conducted at sites with access to 1.5 or 3 Tesla MRI. Patients with no contraindication to MRI as assessed using local institutional protocols, e.g., claustrophobia, metal-containing devices or foreign bodies, will be enrolled.

Two MRIs will be required:

- Baseline: within 7 days of randomization if the patient is randomized within 30 days of the index event or from 7 days before to 30 days after randomization, if the patient is randomized >30 days after the index event. The MRI for the index event may qualify as the baseline MRI, if the imaging was performed within 7 days of randomization.
- Follow-up: within 30 days of EOT visit.

If a recurrent stroke occurs, all information on MRI or CT performed as routine diagnostic will be collected.

Detailed information regarding image acquisition and processing will be found in an MRI Imaging Manual.

A pooling of data from this MRI substudy with substudy data from the ongoing COMPASS study is planned. The later COMPASS MIND MRI substudy will be conducted in 1500 patients with coronary and peripheral artery disease, who receive either aspirin 100 mg o.d., 5 mg rivaroxaban b.i.d., or 2.5 mg rivaroxaban b.i.d. plus aspirin 100 mg o.d.. The 2 substudies will share the set-up, outcome definitions (MRI and cognitive), and MRI Core Facility.

14.1.2 Biomarker substudy

Biomarker samples (plasma, RNA, and DNA) will be collected in this exploratory substudy to promote, facilitate, and improve individualized healthcare by better understanding/predicting ESUS, recurrent stroke, and associated diseases as well as treatment response. Specifically, the intention is to establish ESUS as a distinct clinical entity in which

propensity to coagulation is critical, both as a marker of ESUS and as a risk factor for recurrent stroke.

A total of 18 mL of blood in up to 3000 patients will be collected at the time of randomization for analysis, including, but not limited to: blood biomarker and blood gene expression, as well as genetic determinants.

Biomarkers established in other CV diseases may also play a role in ESUS and recurrent stroke. For example, available data on the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) indicate a link to covert atrial fibrillation. Therefore, potential blood biomarkers that may be measured are: NT-proBNP, hsTroponin, and D-dimer. In addition, other biomarkers of coagulation, pro-thrombotic markers, inflammation markers, and markers linked to stroke or other CV diseases may be analyzed.

Blood gene expression profiles and genetic determinants will be analyzed in a hypothesis free approach with the goal to identify new genes or genetic determinants that are linked to ESUS, recurrent stroke, and other CV diseases.

All genetic information will be doubly de-identified and kept on secure, password protected, computer servers.

Detailed information regarding sampling, processing and storage of blood samples will be found in a Biomarker Manual.

Cover page of the integrated protocol

Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS), comparing rivaroxaban 15 mg once daily with aspirin 100 mg (NAVIGATE ESUS)

For this study, the protocol and subsequent protocol amendments were released as follows:

- Original protocol, Version 1.0, dated 16 JUL 2014
- Amendment 1 for Japan, dated 10 NOV 2014
- Amendment 2 for Ireland dated 16 DEC 2014
- Amendment 3 for South Korea dated 23 JAN 2015
- Amendment 4 for Canada dated 31 MAR 2015
- Global Amendment 5 (described in Section 13.1), forming integrated protocol Version 2.0, dated 05 NOV 2015

This document integrates the original protocol and the global amendment.

Title page

Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS), comparing rivaroxaban 15 mg once daily with aspirin 100 mg (NAVIGATE ESUS)

Secondary prevention of stroke in patients with a recent ESUS

Test drug: BAY 59-7939/rivaroxaban

Clinical study phase: III Date: 05 NOV 2015

EudraCT no.: 2013-000768-27 Version no.: 2.0

Study no.: BAY 59-7939/16573

Sponsor: Bayer HealthCare AG, D-51368 Leverkusen, Germany

Sponsor's medical expert: Calin Pater, MD
Bayer Vital GmbH, 51368 Leverkusen, Germany
Tel. +49 214 30 83505

The study will be conducted in compliance with the protocol, International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) and any applicable regulatory requirements.

Confidential

The information provided in this document is strictly confidential and is intended solely for the guidance of the clinical investigation. Reproduction or disclosure of this document - whether in part or in full - to parties not associated with the clinical investigation, or its use for any other purpose, without the prior written consent of the sponsor is not permitted.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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.



Signature of Bayer's medically responsible person

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

Name: Hardi Mundl, M.D.

Global Clinical Leader

Date:

06 November 2015

Signature:

Hardi Mundl

Signature of the principal investigators for the study

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

Name: Robert G. Hart, M.D.

Co-principal investigator

Affiliation: Professor, Division of Neurology, Department of Medicine,
McMaster University, and Population Health Research Institute,
Hamilton, Canada

Date:

06 November 2015

Signature:

Robert Hart

Name: Stuart J. Connolly, M.D.

Co-principal investigator

Affiliation: Professor, Department of Medicine, McMaster University, and
Population Health Research Institute, Hamilton, Canada

Date:

6/11/15

Signature:

[Signature]

Signature of the principal investigator at the study site

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

Name:

Affiliation:

Date:

Signature:

.....

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

Synopsis - amended

Title	Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS), comparing rivaroxaban 15 mg once daily with aspirin 100 mg (NAVIGATE ESUS)
Short title	Secondary prevention of stroke in patients with ESUS
Clinical study phase	III
Study objectives	<p>The primary efficacy objective is:</p> <ul style="list-style-type: none"> To evaluate whether rivaroxaban is superior to aspirin in reducing the risk of recurrent stroke and systemic embolism in patients with a recent ESUS <p>The secondary efficacy objective is:</p> <ul style="list-style-type: none"> To evaluate whether rivaroxaban is superior to aspirin in reducing cerebrovascular events, cardiovascular events, and mortality in patients with a recent ESUS <p>The safety objective is to document the incidence of clinically relevant bleeding</p>
Study medication	Rivaroxaban 15 mg (immediate-release film-coated tablets), or Aspirin 100 mg (enteric-coated tablets)
Type of control	Double dummy: Matching placebo will be provided for rivaroxaban and aspirin
Route of administration	Study medication is administered orally once daily and should be taken with food
Indication	Secondary prevention of stroke and prevention of systemic embolism in patients with a recent ESUS

Diagnosis and main criteria for inclusion	<p>Recent ESUS (between 7 days and 6 months), defined as:</p> <ul style="list-style-type: none"> • Recent ischemic stroke (including transient ischemic attack with positive neuroimaging) visualized by brain imaging that is not lacunar, and • Absence of cervical carotid atherosclerotic stenosis > 50% or occlusion¹, and • No atrial fibrillation after ≥ 24-hour cardiac rhythm monitoring (at least 20 hours acceptable)², and • No intra-cardiac thrombus on either transesophageal or transthoracic echocardiography,³ and • No other specific cause of stroke (for example, arteritis, dissection, migraine/vasospasm, drug abuse)
Study design	<p>Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study</p>
Methodology	<p>Patients who fulfill all inclusion and none of the exclusion criteria after giving informed consent will be randomly allocated 1:1 to either rivaroxaban 15 mg or aspirin 100 mg orally once daily. Randomization will be stratified by country and age <60 and ≥60 years. ⁴</p> <p>At randomization, patients will receive study medication and instructions for its administration. Thereafter, patients will return to the clinic at 1, 6, and 12 months and then every 6 months until the end of study (efficacy cut-off date) is announced. At 3 months, patients will be contacted by telephone. Throughout the study and at clinic visits, patients will be assessed for efficacy (stroke, systemic embolism, myocardial infarction, cardiovascular death, and all-causes mortality) and safety vital signs, bleeding, serious adverse events which are not outcome events, pregnancies, non-serious adverse events leading to permanent study drug discontinuation, and any non-serious adverse events of particular concern to the investigator).</p> <p>Suspected clinical study outcomes (efficacy and bleeding) will be assessed by an Independent Central Adjudication Committee blinded to treatment allocation. Adjudicated results will be the basis for the final analyses.</p> <p>The study is event-driven and thus, all patients will be treated (or followed-up in case of permanent discontinuation of study medication) until the required approximately 450 confirmed primary efficacy outcomes are expected to have occurred.</p> <p>An Independent Data Monitoring Committee will monitor patient safety during the study and give recommendations to the Steering Committee.</p>

¹ Prior to global Protocol Amendment 5, stenosis was ≥ 50%.

² The phrase in parentheses was added with global Protocol Amendment 5 to reflect routine practice.

³ “Transesophageal” was added with global Protocol Amendment 5.

⁴ The following statement was deleted with global Protocol Amendment 5: “No more than 10% of the total patient population will be randomized into the age group <60 years.” See Section 13.1 for details.

Number of subjects	<p>The study is event-driven and it is estimated that approximately 7000 patients (3500 per treatment group) are to be enrolled in order to have 450 patients experiencing a positively adjudicated primary efficacy outcome event.</p> <p>The number of patients enrolled in the total study may be adjusted or enrollment in the age group 50-59 years may be stopped based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study.⁵</p>
Primary variable	<p>Time from randomization to first occurrence of any of the components of the composite outcome (adjudicated); including:</p> <ul style="list-style-type: none"> • Stroke (ischemic, hemorrhagic, and undefined stroke, transient ischemic attack with positive neuroimaging) • Systemic embolism
Plan for statistical analysis	<p>The primary efficacy analyses will be based on the intent-to-treat population. Rivaroxaban treatment will be compared with the aspirin control 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. Risk reduction will be estimated with the stratified Cox proportional hazards model.</p> <p>Secondary efficacy outcomes will be analyzed using similar methods as for the primary efficacy analysis. Testing will be performed in hierarchical order.</p> <p>There will be 2 formal interim analyses to assess efficacy and stop for overwhelming superiority, which will occur when approximately 50% and 67% of the planned primary efficacy outcomes have accrued.⁶</p> <p>The analysis of the safety outcomes will be similar to those described for the primary efficacy outcome.</p>
Anticipated total study duration and study duration per patient	<p>Total study duration: ~3 years Randomization period: ~2 years Treatment duration of last patient randomized: ~1 year Mean treatment duration per patient: ~2 years</p> <p>The study is event driven and these timelines may vary depending on the enrollment rate and event rate in the study.</p>

⁵ Sentence was revised with global Protocol Amendment 5. See Section 13.1 for details.

⁶ A second interim analysis was added with global Protocol Amendment 5. See Section 13.1 for details.

Table of procedures – amended ⁷

	Screen	Random	Treatment Phase					Washout	
	V1	V2	V3	V4	V5	V6	V7-V [∞]	EOT ^a	Safety Visit
Timelines	-6 to 0 wks ^b	0	1 Mo	3 Mo	6 Mo	12 Mo	every 6 Mo	End of Treat	1 Mo post EOT
Visit Window (weeks)			±1	±4	±4	±4	±4		±1
Type of Visit	Visit	Visit	Visit ^L	☎	Visit	Visit	Visit	Visit	☎
Initiation procedures									
Informed consent	•								
Eligibility criteria	•								
Demographics	•								
Medical history and stroke risk factors	•								
Treatment and diagnosis of stroke ^c	•								
Pregnancy test ^d	•								
eGFR ^e	•								
Weight/height ^f	•					•	□		
Medication									
ConMeds ^g		•				•	□	•	
1 st study drug		•							
Drug dispense		•			•	•	•	•	
Drug return + accountability		•			•	•	•	•	
Efficacy/Safety Outcomes ^h			← continuous reporting →						
Safety			← continuous reporting →						
Adverse events ⁱ									
Vital signs ^j		•			•	•	□	•	
Outcomes Research									
EQ-5D		•			•	•	•	•	
MoCA and SAGE		•				•	•	•	
Modified Rankin Score ^k	•					•		•	

Abbreviations: EOT = end of treatment; Mo = month; V = visit, ☎ = telephone contact; eGFR = estimated glomerular filtration rate; ConMeds = Concomitant medications; MoCA = Montreal Cognitive Assessment; SAGE = Standard Assessment of Global-Activities in the Elderly; EQ-5D = European Quality of Life-5 Dimensions questionnaire; SAE = serious adverse event; TIA = transient ischemic attack; MI = myocardial infarction

- a End of treatment visit is to be performed within the trial close-out window before the end of the study (efficacy cut-off date) or once the patient has permanently discontinued study medication and when no further visits at the site will be performed
- b Screening visit can be the same as randomization visit, if all required tests for eligibility criteria are available at screening visit. Maximum screening period 6 weeks.
- c Acute and chronic therapy of stroke (for example [e.g.], thrombolysis, aspirin [ASA]) and diagnostic tests performed to diagnose acute stroke and Embolic Stroke of Undetermined Source (ESUS) as well as National Institutes of Health Stroke Score (NIHSS)

⁷ Global Protocol Amendment 5 made the following changes to this table: the Digit Symbol Substitution (DSS) test was removed; the window for Visit 1 was extended 2 weeks; footnotes a, b, and k were revised; and footnote L was added. See Section 13.1 for details.

-
- d Only in women of childbearing potential (local urine or serum pregnancy test)
 - e Creatinine to be measured at the local laboratory at screening, unless conducted within 1 month prior to screening. The eGFR may be recorded as reported by the local laboratory or otherwise should be calculated using Modification of Diet in Renal Disease (MDRD) formula. A calculator may be found at www.mdrd.com. During the study creatinine and eGFR should be measured according to local practice.
 - f Height to be measured only at screening
 - g Concomitant medications and the changes need to be documented only at the specified visits for chronic cerebro- and cardiovascular treatments. In addition, treatments for SAEs and outcome events must be reported.
 - h All potential outcome events including recurrent stroke, TIA, systemic embolism, MI, hospitalizations for cardiac chest pain, deaths, and bleeding must be reported on an ongoing basis even if the patient is permanently discontinued from study treatment. Healthcare resource use will be documented for all endpoints. See Section 7.6.1.1
 - i Only SAEs not exempted from SAE reporting, pregnancy, non-serious AE leading to permanent discontinuation, and non-serious AEs of particular concern to the investigator need to be reported. See Section 7.5.3.2.
 - j Blood pressure and heart rate
 - k For definition see Section 7.6.1.4. In case of recurrent stroke to be done at 7 days post stroke or at discharge from hospital in case this occurs before 7 days and again at 3-6 months post stroke
 - L Patients who are at a rehabilitation or other clinic at the time of the 1 month visit (Visit 3), more flexibility will be allowed and this visit can be performed as a phone call instead of an onsite visit.
 - To be performed at specified visits
 - To be performed only once per year

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List of abbreviations

ACS	Acute coronary syndrome
AE	Adverse event
AF	Atrial fibrillation
APCC	Activated prothrombin complex concentrate
ARISTOTLE	Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE)
ASA	Acetylsalicylic acid; aspirin
AVERROES	A Phase III Study of Apixaban in Patients With Atrial Fibrillation (AVERROES)
BHC	Bayer HealthCare
b.i.d.	Twice daily
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence interval
ConMed	Concomitant medication
CRO	Contract research organization
CT	Computed tomography
cTn	Cardiac troponin
CV	Cardiovascular
CYP3A4	Cytochrome P450 isoenzyme 3A4
DSS	Digit Symbol Substitution test
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EINSTEIN	Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis -The EINSTEIN DVT Study
e.g.	for example
eGFR	Estimated glomerular filtration rate
ENGAGE	Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (EngageAFTIMI48)
EOT	End-of-treatment
EQ-5D	European Quality of Life-5 Dimensions questionnaire
ESUS	Embolic stroke of undetermined source
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
H	hypothesis
HDPE	High-density polyethylene
HR	Hazard ratio
ICAC	Independent Central Adjudication Committee
ICF	Informed consent form
ICH	International Conference on Harmonisation

IB	Investigator's brochure
i.e.	id est (that is)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	International ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-to-treat
IxRS	Interactive web/voice response system
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
Mo	Month
MoCA	Montreal Cognitive Assessment
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Score
NSAID	Non-steroid anti-inflammatory drug
NV	Corporation (in The Netherlands)
NVAF	Non-valvular atrial fibrillation
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
o.d.	Once daily
OMP	Ortho McNeil Pharmaceuticals
p	p-value
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PE	Pulmonary embolism
P-gp	P-glycoprotein
PICCS	Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS)
PID	Patient identification
PPS	Per protocol set
PT	Prothrombin time
PV	Pharmacovigilance
QA	Quality assurance
ROCKET AF	An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation
RRR	Relative risk reduction
S	survival
SAE	Serious adverse event
SAF	Safety data set
SAGE	Standard Assessment of Global-Activities in the Elderly
SAP	Statistical analysis plan

SC	Steering Committee
SUSAR	Suspected unexpected serious adverse reaction
TIA	Transient ischemic attack
USA	United States of America
TOAST	Trial of Org 10172 in Acute Stroke Treatment
V	Visit
VKA	Vitamin K antagonist
vs.	versus
VTE	Venous thromboembolism
WARSS	Warfarin-Aspirin Recurrent Stroke Study
WHO	World Health Organization
WMH	White matter hyperintensities

1. Introduction

1.1 Background

Globally, cerebrovascular disease (stroke) is the second leading cause of death (1) and the fourth leading cause of disease burden as measured in disability-adjusted life years. (2) The World Health Organization (WHO) estimates that worldwide 16 million people suffer a first ever stroke annually, with 5 million deaths due to stroke in 2005, and another 5 million left permanently disabled. (3)

The incidence of stroke is declining in many developed countries, largely as a result of better control of high blood pressure and reduced levels of smoking. However, the absolute number of strokes continues to increase because of the ageing population. In the absence of additional population-wide interventions, the numbers are expected to rise to 18 million first-ever strokes and 6.5 million deaths in 2015 and 7.8 million deaths in 2030.

Approximately two-thirds of patients are left with physical or cognitive disabilities. Stroke costs the United States (US) an estimated \$54 billion each year. (4) In the US, 75% of all strokes are first or new strokes and 25% are recurrent strokes. (5)

About 87% of all strokes are of ischemic origin. Sub-types of ischemic stroke are defined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. (6)

Approximately 30% of all ischemic strokes are due to arteriosclerosis of the intra- and extracranial large arteries; 20 % are lacunar, i.e., due to small artery disease; 20% have a cardioembolic source such as atrial fibrillation; and 5% are classified as “unusual” (for example [e.g.], dissections, arteritis). For the remaining 25% of strokes, the term ‘Cryptogenic Stroke’ has been used to describe patients with ischemic stroke in whom there is no clear etiology. (7) In cryptogenic stroke the source of embolism or thrombosis cannot be readily determined in each and every patient, and in fact, it is not uncommon to identify more than one potential cause in the individual patient.

1.2 Embolic stroke of undetermined source

Recently, the concept of “embolic stroke of undetermined source” (ESUS) has developed, recognizing that except for lacunar strokes, most cryptogenic strokes are embolic.(7) The sources of embolism underlying ESUS include the heart (either within the heart or via paradoxical embolism from a venous source), aortic arch, or the large cervical and cerebral arteries.

Investigations to establish a diagnosis of ESUS involves exclusion of lacunar stroke and stroke related to severe occlusive atherosclerotic disease of intra- and extracranial large arteries. Lacunar strokes need to be excluded, as the great majority of these are due to in-situ thrombosis on microatheroma or non-thrombotic occlusions of small cerebral arteries. Newly detected, previously unrecognized, major-risk cardioembolic sources such as atrial fibrillation and left ventricular thrombus that warrant anticoagulation therapy must also be excluded.

In summary, ESUS is defined as a non-lacunar brain infarct without proximal arterial stenosis or major-risk cardioembolic sources that have a clear indication for anticoagulation.

1.3 Studies assessing the efficacy of anticoagulation for secondary prevention of embolic stroke of undetermined source - amended

The only available randomized clinical trial data in patients with cryptogenic stroke stem from a subgroup analysis in the Warfarin-Aspirin Recurrent Stroke Study (WARSS; 1993-2000),⁽⁸⁾ where patients were randomly assigned to aspirin (acetylsalicylic acid; ASA) 325 mg once daily (o.d.) or warfarin (target International Ratio [INR] 1.4 to 2.8). This subgroup included 576 out of the 2206 patients. Cryptogenic stroke was based on the TOAST criteria ⁽⁶⁾ (2 or more causes identified or a negative evaluation, or an incomplete evaluation) ^(7,9). The primary outcome of ischemic stroke or death occurred in 15.0% assigned to warfarin vs. 16.5% assigned to ASA over two years (Hazard Ratio [HR] 0.92, 95% Confidence Interval [CI] 0.6-1.4). ⁽⁹⁾ The INRs achieved were relatively low (median achieved INR = 1.9) and were a noteworthy reflection of the relative efficacy of anticoagulation vs. antiplatelet agents in patients with cryptogenic stroke. The rates of major hemorrhage were low (2.22 per 100 patient-years in the warfarin group and 1.49 per 100 patient-years in the ASA group).

For 338 participants with cryptogenic stroke whose computed tomography (CT) showed an “embolic topography” the 2 year rate of recurrent ischemic stroke or death was 12% with warfarin vs. 18% with ASA (HR=0.66, 95% CI 0.4-1.2). ⁽⁹⁾

In summary, despite a low therapeutic warfarin anticoagulation range (median INR = 1.9) and limited statistical power, WARSS data from a randomized comparison support the concept that anticoagulation may be substantially more efficacious than ASA for patients with cryptogenic ischemic stroke with embolic features (i.e., those comparable to ESUS patients). In addition, in the PICSS study, 98 participants with a patent foramen ovale, the primary outcome (2 year rate of recurrent ischemic stroke or death) was halved in those assigned to warfarin (9.5% warfarin vs. 17.9% ASA).⁸ ⁽¹⁰⁾

Vitamin K antagonists (VKAs) are not routinely used for cryptogenic stroke/ESUS. A Cochrane Collaboration meta-analysis of trials for secondary prevention in patients with a history of non-cardioembolic stroke of various causes, such as large artery atherosclerosis, intracranial artery stenosis, small penetrating artery disease, and strokes of unknown cause (i.e., cryptogenic stroke) suggested that higher intensity anticoagulation with VKAs could be associated with higher all-cause mortality and major bleeding events. ⁽¹¹⁾

1.4 Efficacy and safety of rivaroxaban in patients with prior stroke

Rivaroxaban is an oral, highly selective direct Factor Xa inhibitor. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi.

Rivaroxaban has been tested in interventional and non-interventional trials involving more than 70,000 patients and the cumulative worldwide exposure during 5.5 years of marketing (since SEP 2008) is estimated at approximately 2.4 million patient years in approximately 8 million patients treated overall. Rivaroxaban is approved in adults for the prevention of

⁸ Data in this sentence were corrected with global Protocol Amendment 5. See Section 13.1.2 for additional details.

venous thromboembolism (VTE) following elective hip or knee replacement surgery, treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE. It has been approved in the European Union (EU) and other countries for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers when co-administered with ASA or ASA plus clopidogrel or ticlopidine.

Rivaroxaban is also approved for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAf) with one or more risk factors. Approval was based on the ROCKET-AF trial, (12) in which rivaroxaban was shown to be non-inferior to warfarin. There was also no significant between-group difference in the risk of major bleeding. A pre-specified subgroup analysis showed that the efficacy and safety of rivaroxaban compared with warfarin among patients with and without a previous transient ischemic attack (TIA) or ischemic stroke was consistent. (13)

A major advantage of the novel oral anticoagulants over warfarin that emerged from recent phase III randomized clinical trials involving non-valvular atrial fibrillation patients is the reduced risk of intracranial hemorrhage. (12,14,15) In the ROCKET-AF trial, intracranial hemorrhage was reduced (HR 0.67; p=0.02) by rivaroxaban relative to warfarin. (12)

Prior stroke is a risk factor for intracerebral hemorrhage during warfarin anticoagulation. In ROCKET-AF, there was no significant interaction between prior stroke and relative effect of rivaroxaban vs. warfarin on hemorrhagic stroke. (13) While patients with recognized AF will be excluded from the proposed trial, the cause of ESUS in many patients is unrecognized cardiogenic embolism, including undiagnosed paroxysmal atrial fibrillation, and hence these observations may be relevant.

Patients with cryptogenic ischemic stroke are likely to have a higher risk of intracranial hemorrhage than patients with vascular disease without prior stroke/TIA. The absolute rate of intracranial hemorrhage in patients with cryptogenic ischemic stroke, if given rivaroxaban, is likely to be less than that observed in ROCKET-AF participants with prior stroke/TIA (0.59%/year). This is due to a lower average age of patients with cryptogenic stroke (a powerful independent risk factor for intracranial hemorrhage [16]) compared with the high risk ROCKET-AF population.

The only large-scale comparison of a novel oral anticoagulant (apixaban) with ASA, the AVERROES study, involving patients with NVAf who were unsuitable to VKA treatment was stopped prematurely by the Independent Data Monitoring Committee (IDMC) for overwhelming efficacy. (17) A significant reduction in the primary efficacy outcome (stroke and systemic embolism) was reported for all patients (HR 0.45) and in the patients with previous stroke or TIA the HR was 0.29. (18) Major bleeding was more frequent in patients with a history of stroke or TIA than in patients without (HR 2.88) but the overall risk for these events was small and only slightly more reported in the apixaban group (44 vs. 39 events, HR 1.13). There was also no difference in intracranial bleeding with apixaban vs. ASA, albeit based on a relatively small number of events (apixaban = 11, ASA = 13). (17) In a recent comprehensive meta-analysis, based on indirect comparison, the risk of subdural hematoma (comprising 30% of intracranial hemorrhages) was equal comparing oral factor Xa inhibitors with ASA. (19) Consequently, intracranial hemorrhage is unlikely to limit a

comparison of rivaroxaban with ASA for secondary prevention of stroke in patients with ESUS.

1.5 Current guideline recommendations and dose of aspirin

The 2008 American College of Chest Physicians guideline and 2008 American Heart Association guideline specifically recommended antiplatelet therapy for patients with cryptogenic ischemic stroke. (20, 21) The 2008 European Stroke Organization guideline, the 2014 American Heart Association revised guideline, the 2012 American College of Chest Physicians guideline, and the 2008 Canadian Best Practice Recommendations for Stroke Care do not comment specifically on cryptogenic stroke, but recommend antiplatelet therapy for patients with non-cardioembolic ischemic stroke. (22-25) These are primarily Grade 1A/(Class I, Level of Evidence A) recommendations. Aspirin is the drug most frequently used. A daily dosage range of 50 mg to 325 mg of ASA is recommended in current guidelines, although the data for doses < 75 mg are limited. An ASA dosage of 100 mg daily is included in most major guidelines and is acceptable to most clinicians around the world. Guidelines recommend initiation of ASA immediately after brain imaging has excluded intracerebral hemorrhage, if the patient can swallow, and this is standard of care. The long-term (> 5 years) treatment is recommended. (25)

1.6 Study rationale

Randomized clinical trials have addressed secondary prevention for all major ischemic stroke subtypes except for cryptogenic stroke or ESUS. Among the estimated 300,000 patients with acute cryptogenic stroke annually in North America and Europe there has been little progress in secondary prevention during the past two decades. There is a substantial unmet medical need in this patient population, as despite treatment with antiplatelets, the recurrent stroke rate still remains at 3 to 6% annually. (7)

There is persuasive evidence that the dominant underlying pathophysiology of ESUS is embolism (cardioembolic, arteriogenic, or paradoxical). Improvements in imaging technology and an increased appreciation of the underlying pathophysiology of ESUS have resulted in better understanding and in a practical clinical definition of ESUS (7) so that these patients can be reliably identified.

Based on evidence for superior efficacy of warfarin anticoagulation over ASA for other types of embolic stroke, anticoagulation is expected to be superior to ASA in ESUS patients. The direct oral Factor Xa-inhibitor rivaroxaban, when compared with VKAs, has been demonstrated to be effective against embolic stroke related to non-valvular AF. Because of its predictable anticoagulant activity and low risk of intracranial hemorrhage, it is expected that rivaroxaban will reduce stroke recurrence in ESUS compared with ASA, and with an acceptable safety (bleeding) profile. Rivaroxaban has also been shown to be efficacious for the treatment of DVT and PE, prevention of recurrent DVT and PE, prevention of VTE following total hip and total knee replacement, and also for prevention of atherothrombotic events after an ACS with elevated cardiac biomarker. Rivaroxaban has no dietary restrictions and only few drug interactions and does not require routine coagulation laboratory monitoring.

Given these considerations, a large, multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study comparing rivaroxaban 15 mg o.d. with ASA 100 mg o.d. for the secondary prevention of stroke and prevention of systemic embolism will be conducted.

1.7 Dose rationale

This will be the first study investigating rivaroxaban for secondary prevention of stroke in patients with ESUS.

Data in patients with NVAF in the ROCKET-AF study with rivaroxaban as well as data from other new oral anticoagulants (apixaban, dabigatran, edoxaban) and Vitamin K antagonists give support for the benefit of rivaroxaban in this indication, as in both patient populations strokes are primarily of thromboembolic origin. Apixaban, one of the Factor Xa inhibitors showed superiority to ASA (AVERROES study). However, studies comparing anticoagulants to antiplatelets have shown higher bleeding rates.

We assume that in the proposed study rivaroxaban 15 mg will reduce recurrent stroke and systemic embolism as compared to ASA 100 mg. 15 mg is expected to show significant efficacy combined with an acceptable bleeding profile for the following reasons:

- A dose as high as 20 mg as used in embolic stroke prevention in patients with non-valvular atrial fibrillation (ROCKET AF study) might not be necessary for efficacy
 - Modelling data show an overlap of exposure (rivaroxaban plasma concentrations over time) for 15 mg with 20 mg rivaroxaban
 - 15 mg was effective and safe in ROCKET AF in patients with moderate renal impairment and J-ROCKET in patients with normal/mild renal impairment
- 15 mg rivaroxaban will likely lead to less bleeding compared to 20 mg, which is important in an ESUS population that is more vulnerable for intracranial hemorrhage

Because the dose selected for this study is already an adjustment down from the dose used for stroke prophylaxis in NVAF, a dose adjustment for patients with moderate-severe renal impairment is not considered necessary.

1.8 Benefit/risk assessment

Worldwide, 16 million people suffer a first ever stroke annually and 25% of all ischemic strokes are recurrent strokes. The ischemic stroke recurrence rate is substantial and remains at 3 to 6% per year during ASA treatment, the standard guideline recommended antithrombotic therapy for secondary prevention in most patients without major-risk cardioembolic causes.

No specific treatment has been tested for patients with ESUS. Only recently have insights into this disease revealed that most of these strokes are due to embolism. Data from the WARSS study and clinical trials with oral anticoagulants in patients with non-valvular atrial fibrillation support that anticoagulation is likely to be the better treatment option for embolic stroke compared with antiplatelet therapy. Based on these findings, it is expected that the

NAVIGATE ESUS trial will show that rivaroxaban is superior to ASA for secondary prevention of stroke in patients with ESUS.

Rivaroxaban has been well tolerated in all studies conducted to date. The main safety finding is bleeding, a recognized complication shared by all anticoagulants. Occurrence of major bleeding is relatively low and importantly, intracranial bleeding was substantially lower in patients receiving rivaroxaban compared to warfarin in the ROCKET-AF study.

The 15 mg o.d. dose for rivaroxaban has been selected to balance benefit and risk for ESUS patients treated in the study.

Approximately 25% of the worldwide stroke incidence is caused by ESUS. If the results of this trial, which will focus on this population of patients, favor the use of rivaroxaban, millions of patients could benefit from this treatment.

2. Study objectives

The primary efficacy objective is:

- To evaluate whether rivaroxaban is superior to aspirin in reducing the risk of recurrent stroke and systemic embolism in patients with a recent ESUS

The secondary efficacy objective is:

- To evaluate whether rivaroxaban is superior to aspirin in reducing the risk of cerebrovascular events, cardiovascular events, and mortality in patients with a recent ESUS

The safety objective is to document the incidence of clinically relevant bleeding.

3. Investigators and other study personnel

3.1 Investigator

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 sheet before patient recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center.

3.2 Study personnel

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

3.3 Study committees

Separate charters will be prepared for all study committees overseeing the study including the personnel, responsibilities, procedures, and meeting frequencies.

3.3.1 Steering Committee

The Steering Committee (SC) will consist of the 2 co-principal investigators, National Leaders from all countries, and sponsor representatives. The SC 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 SC will convene regularly to discuss and report on ongoing supervision of the study.

3.3.2 Independent Data Monitoring Committee

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 and/or cardiovascular disease, and biostatistics; and who are not members of the SC, or involved as investigators or otherwise in the trial.

3.3.3 Independent Central Adjudication Committee

The Independent Central Adjudication Committee (ICAC) will comprise members with clinical and methodological expertise in neurology and cardiology who will be responsible for adjudication and classification of outcome events in the study.

4. Study design

4.1 Overview

This is a multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study in patients with a recent ESUS.

Following provision of informed consent, patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomly allocated by an interactive voice/web response system (IxRS) to either rivaroxaban 15 mg o.d. or ASA 100 mg o.d. in a 1:1 ratio. No dose adjustment will be made for patients with mild or moderate renal impairment.

Patients may be randomized and receive the first study medication intake between 7 days and 6 months after the index stroke event. In case of minor strokes (National Institutes of Health Stroke Score [NIHSS] ≤ 3), study medication may be initiated as early as 3 days after stroke onset if all eligibility assessments have been completed. In the presence of hemorrhagic transformation on the qualifying brain imaging study or if intravenous thrombolysis therapy was given for the index stroke, study medication will not be initiated before 10 days after the acute stroke event unless a repeat CT or magnetic resonance imaging (MRI) performed before randomization documents the absence of new or extension of hemorrhage.

Patients will be randomized⁹ as early as possible after the required diagnostic evaluation is complete and eligibility criteria are fulfilled. The goal is that the majority of patients are enrolled within 3 months, and fewer patients between 3 and 6 months.

Randomization will be stratified by country and age <60 and ≥ 60 years. Patients < 60 years will need to have at least one risk factor such as stroke (includes covert/silent strokes on

⁹ Prior to global Protocol Amendment 5, “randomized” was “enrolled.”

neuroimaging) or TIA prior to index stroke, diabetes, hypertension, current tobacco smoker or heart failure.¹⁰

At randomization, patients will receive study medication and instructions for its administration. Thereafter, patients will return to the clinic at 1, 6, and 12 months and then every 6 months until the end of study (efficacy cut-off date) is announced. At 3 months, the patient will be contacted by telephone. Throughout the study and at clinic visits, patients will be assessed for efficacy (stroke, systemic embolism, MI, CV death, or all-cause mortality) and safety (vital signs, bleeding, serious adverse events [SAEs] which are not outcome events, non-serious adverse events [AEs] leading to permanent discontinuation of study treatment, and any non-serious AEs of particular concern to the investigator).

The trial will continue until approximately 450 patients are anticipated to have experienced a positively adjudicated primary efficacy outcome event. This is anticipated to occur approximately 3 years after the first patient is randomized, but may vary depending on the recruitment rate as well as the primary event rate. A telephone safety visit will be performed 1 month after the end-of-treatment (EOT) visit.

Patients permanently discontinuing study treatment will continue to be followed, and outcome events and vital status must be assessed in these patients until the end of the study via either clinic visits or telephone contacts.

All efficacy and safety analyses are based on time from randomization to time of first event. Suspected clinical study outcomes will be assessed by the ICAC, which will be blinded to treatment allocation. Adjudicated results will be the basis for the final analyses. The IDMC will monitor patient safety during the study and give recommendations to the SC and sponsor.

A schematic of the study design is provided in [Figure 4–1](#).

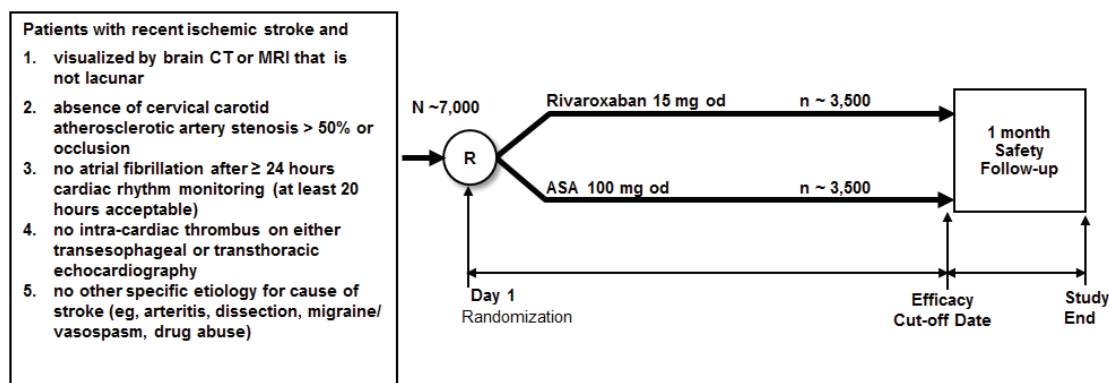


Figure 4–1: Study design schematic - amended

¹⁰ Paragraph revised with global Protocol Amendment 5. See Section 13.1 for details.

4.2 Justification of the design

The target patient population comprises patients with a recent ESUS. These patients have substantial risk for recurrent stroke and other thromboembolic events despite antiplatelet therapy, the current standard of care. A double-blind, randomized trial design comparing rivaroxaban with ASA is deemed the most appropriate design to allow for an unbiased evaluation of rivaroxaban as a treatment option for this patient population in an international trial.

4.3 End of study

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 final efficacy outcome event has been adjudicated for patients from all participating clinical sites (EU and non-EU).

5. Study population – amended

This Phase III, multi-national, study will be conducted in approximately 30 countries¹¹ worldwide in approximately 7000 patients recruited primarily from hospital-based stroke units. Patients who will be enrolled in this study must meet all of the inclusion criteria and none of the exclusion criteria listed in Section 5.1.

5.1 Eligibility

5.1.1 Inclusion criteria - amended

1. Embolic stroke of undetermined source (ESUS) defined as:

- Recent ischemic stroke (including TIA with positive neuroimaging) visualized by brain CT or MRI that is not lacunar (i.e., lacunar infarcts are subcortical infarcts ≤ 1.5 cm in the territory of middle cerebral artery or pons; infarcts involving the cerebellum or lateral medulla are not considered as lacunar infarcts). Patients with multiple simultaneous acute lacunar infarcts on DWI imaging may be included. In case of embolic large artery occlusions clearly documented on angiography who undergo successful recanalization, visualization of infarct on neuroimaging is not mandated¹², and
- Absence of cervical carotid atherosclerotic stenosis (or vertebral and basilar artery atherosclerotic stenosis in case of posterior circulation stroke), that is $> 50\%$, or occlusion in arteries supplying the area of ischemia in CT or magnetic resonance (MR) angiography or conventional angiography or ultrasound, and¹³

¹¹ Was 25 to 30 countries prior to global Protocol Amendment 5.

¹² Text was revised with global Protocol Amendment 5. See Section 13.1 for details.

¹³ Bulleted text was revised with global Protocol Amendment 5. See Section 13.1 for details.

- No history of AF, no documented AF on 12-lead electrocardiogram (ECG) or episode of AF lasting 6 minutes or longer detected after \geq 24-hour cardiac rhythm monitoring (Holter or telemetry; at least 20 hours acceptable¹⁴), and
 - No intra-cardiac thrombus on either transesophageal or transthoracic echocardiography¹⁵, and
 - No other specific cause of stroke identified by routine clinical care (e.g., arteritis, dissection, migraine/vasospasm, drug abuse)
2. Time from recent ischemic stroke to randomization and first study medication intake (and only if the investigator regards it as safe to initiate therapy with an anticoagulant) between 7 days and 6 months except:
 - in case of minor strokes (NIHSS \leq 3), study medication may be initiated as early as 3 days after stroke onset.
 - in case of intravenous thrombolysis treatment or hemorrhagic transformation seen on the qualifying CT or MRI, study medication will not be initiated before 10 days after the acute stroke event unless a repeat CT or MRI scan performed before randomization documents the absence of new or extension of hemorrhage.
 3. All planned diagnostic tests for stroke evaluation must be completed. Brain imaging and 24-hour cardiac monitoring must be repeated if new symptoms of stroke/TIA occurred after the initial stroke evaluation, as does 24-hour cardiac monitoring if symptoms suggestive of AF occur.
 4. Age \geq 50 years ¹⁶
 5. For patients with age 50-59 years at least one of the following risk factors: stroke or TIA prior to index stroke (includes covert/silent strokes on neuroimaging), diabetes, hypertension, current tobacco smoker, or heart failure.¹⁷
 6. Written informed consent consistent with local regulations governing research in human subjects

5.1.2 Exclusion criteria - amended

1. Severely disabling stroke (modified Rankin score \geq 4 at screening)
2. If imaging of intracranial arteries is performed by CT or MR angiography or transcranial Doppler: $>$ 50% luminal stenosis or occlusion in arteries supplying the area of ischemia¹⁸
3. Patent foramen ovale with plans for closure
4. Known serious infection or inflammatory disease that may be the cause of stroke

¹⁴ Global Protocol Amendment 5 added the allowance of monitoring for at least 20 hours to reflect routine practice.

¹⁵ Transesophageal was added with global Protocol Amendment 5.

¹⁶ Prior to global Protocol Amendment 5, patients were eligible for inclusion if they were \geq 18 years of age (or $>$ 18 years based on country). See Section 13.1.1 for additional details.

¹⁷ This criterion was revised with global Protocol Amendment 5. See Section 13.1 for details.

¹⁸ Prior to global Protocol Amendment 5, luminal stenosis or occlusion was \geq 50%. See Section 13.1 for details.

5. Patient has or is intended to receive an implantable ECG loop recorder
6. Indication for chronic anticoagulation based on guideline recommendations or investigator's judgment; e.g., patient with prosthetic mechanical valve, venous thromboembolism, hypercoagulable state
7. Indication for chronic antiplatelet therapy based on investigator's judgment, in which anticoagulation is not a reasonable substitute, or chronic therapy with a conventional non-steroid anti-inflammatory drug (NSAID) for a non-stroke indication
8. Hypersensitivity or any other contraindication listed in the local labeling for ASA or rivaroxaban
9. Active bleeding, major bleeding within last 6 months, high risk for serious bleeding contraindicating anticoagulant or antiplatelet therapy or history of primary intracranial hemorrhage¹⁹
10. Hepatic disease associated with coagulopathy (prothrombin time prolonged beyond the normal range) and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
11. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² as assessed at local laboratory within 1 month of screening
12. Life expectancy less than 6 months
13. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), i.e., human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, or posaconazole, if used systemically
14. Female of childbearing potential who are not surgically sterile, or, if sexually active not willing to use adequate contraceptive measures with a failure rate less than 1% per year (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, male partner sterilization) before entry and throughout the study, as well as pregnant or breast feeding women
15. Inability to cooperate with the study procedures
16. Previous randomization to this study or participation in a study with an investigational drug or medical device within 30 days prior to randomization
17. 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)

5.2 Discontinuation of patients from study treatment - amended

An excessive rate of patient discontinuations from either treatment or “drop-outs” from the study may render the trial non-interpretable. In this study, outcome 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 will be taken to**

¹⁹ Criterion revised with global Protocol Amendment 5. See Section 13.1 for details.

motivate patients to comply with all study procedures and to continue to be followed until the end of the trial.

Patients may discontinue study medication at their own request and without giving reasons (even though providing a reason is encouraged), based on the investigator's judgment, if the patient is pregnant, or at the request of the sponsor (exceptional circumstances). In case a patient is diagnosed with atrial fibrillation with an episode of at least 6 minutes during the study trial medication must be stopped (see section 6.9.2).²⁰ **Study drug will not be routinely discontinued in participants reaching a potential outcome event unless there is a safety concern or a clear indication for an alternative antithrombotic therapy as determined by the local investigator.**

In case of a temporary study medication interruption²¹ for any reason, study medication will be restarted as soon as medically justified in the opinion of the investigator. There is no defined maximum limit for temporary treatment interruption.

For all patients who permanently discontinue study medication, the patients will still be part of the study, and outcome events and vital status must be reported until the efficacy cut-off date for the study is announced. All safety data will continue to be collected for 1 month after the last study medication intake (safety follow-up visit). The investigator and patient must discuss and determine further follow-up options. Options for follow-up are listed below, in descending order of preference:

1. Patient continues the regular study clinic visits at the investigator's site as outlined in the protocol
2. Patient will be contacted by phone at the regular follow-up intervals
3. Patient allows his/her general practitioner or a family relative to be contacted (if allowed in respective country) at the regular follow-up interval
4. Patient will be contacted once at the end of the study
5. Patient withdraws consent. This will be the last option and means that the patient does not agree to any kind of follow-up and specifically refuses any further contact with the investigator. This should happen only in exceptional cases. If possible by local regulations, this decision will be provided in writing. Vital status will be obtained at study end through public information according to local guidelines and as allowed by local regulations.

For patients who do not agree to attend regular study visits, the investigator will encourage the patient to return to the clinic for at least one final visit in order to perform all assessments as outlined for the EOT visit.

If a patient fails to return for a study visit or is lost-to-follow-up, the investigator should explore all possible options to contact the patient. In that respect, the investigator should ask the patient at the study start for the contact details of a relative or friend who can be contacted in case the patient cannot be reached. The site must document all attempts to try to contact the patient in the medical records/source documents. If all attempts fail, depending on local

²⁰ Global Protocol Amendment 5 added "with an episode of at least 6 minutes" to this sentence.

²¹ Prior to global Protocol Amendment 5, "interruption" had been "discontinuation."

legislation, death registries or other registries may be accessed or private investigation to locate a patient may be initiated.

If study medication is temporarily interrupted or permanently discontinued, the investigator will document the reason for in the medical records and on the electronic case report form (eCRF).²²

5.3 Patient 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 time of randomization. This randomization number will allow subsequent identification of treatment allocation.

6. Treatments

6.1 Treatments to be administered

The treatments to be administered are rivaroxaban 15 mg o.d. or ASA 100 mg o.d..

6.2 Identity of study treatment

All study drugs 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.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance (QA) group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor study file.

6.3 Treatment assignment - amended

Patients will be randomly assigned to treatment in a blinded manner to one of 2 study arms:

- Rivaroxaban plus placebo ASA
- ASA plus placebo rivaroxaban

Allocation to treatment will be done centrally by IxRS. Allocation will be performed in a 1:1 ratio to each study treatment and will be stratified by country and by age (<60 or ≥60 year).

Specific procedures for treatment assignment through the IxRS are described in the IxRS manual.²³

²² Global Protocol Amendment 5 deleted the following sentence from this section: "Patients who permanently discontinue the study for any reason will not be reactivated" because this section covers discontinuation of study treatment, not study, and this point is covered by exclusion criterion 16.

6.4 Dosage and administration

Patients will be provided with a high-density polyethylene (HDPE) -bottle containing immediate-release film-coated tablets of rivaroxaban 15 mg or matching placebo and an HDPE bottle containing enteric-coated tablets of ASA 100 mg or matching placebo.

One tablet from each bottle should be taken once daily with food. If a dose is missed the patient should take study medication immediately and continue on the following day with the once daily intake. The dose should not be doubled within the same day to make up for a missed dose.

6.5 Blinding

The study is double-blinded using matching placebo medication as described in Section 6.4.

6.5.1 Emergency unblinding by the investigator - amended

Unnecessary unblinding should be avoided and should only be undertaken by the investigator or the treating physician when it is essential for the patient's safety. In such a situation, the investigator will be able to unblind the patient via the country toll-free help line.²⁴

Investigators will be provided with the details on the emergency unblinding procedure at study start.

For unblinding in case of a Suspected Unexpected Serious Adverse Reaction (SUSAR) see Section 7.5.3.2.

6.6 Drug logistics and accountability

Study medication will be provided by Bayer and labeled according to local law and regulation. A complete record of batch numbers, expiry dates and labels will be maintained in the study file.

All study medication needs 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 should not be stored above 30°C. The study drug is to be kept in a secure area (e.g., locked cabinet) without access to unauthorized personnel. Site personnel will confirm receipt of study medication via IxRS and will use study medication only for this study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study medication must be properly documented according to local regulation and specified procedures.

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

²³ The following sentence was deleted from this section with global Protocol Amendment 5: "No more than 10% of the total patient number will be randomized into the age group <60 years." See Section 13.1 for details.

²⁴ This paragraph was revised with global Protocol Amendment 5. See Section 13.1 for details.

6.7 Treatment compliance - amended

Compliance will be evaluated by interview and by counting the tablets returned by the patient to the site versus the tablets expected to be taken by the patient.

First dose, last dose, and any dose interruptions of study medication due to AEs, study outcome events,²⁵ or of >7 days for any other reason will be reported in the eCRF.

6.8 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.

6.9 Prior and concomitant therapy - amended

Acute and chronic therapies given for the qualifying stroke will be recorded in the eCRF. During the study, chronic concomitant therapy will be recorded at the visits (cerebro- and cardiovascular therapies) or at the time of occurrence of any efficacy outcome, bleeding, or SAE.

For patients at risk of 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 by the study.

²⁶No specific concomitant medications are prohibited other than strong inhibitors of both CYP3A4 and Pgp inhibitors. This includes human immunodeficiency virus protease inhibitors and the following azole antimycotics agents: ketoconazole, itraconazole, voriconazole, or posaconazole, if used systemically. However, fluconazole is allowed.

In addition, concomitant use with antiplatelets and anticoagulants is outlined in the sections below.

6.9.1 Guidance for management of participants who require antiplatelet therapy or non-steroidal anti-inflammatory drug during the study

Patients who enter the study receiving antiplatelet therapy (e.g., ASA) will have non-study antiplatelet therapy discontinued when study medication is started.

The concomitant use of NSAID and non-study antiplatelet therapy during the study is strongly discouraged since it increases the risk for bleeding. However, if a NSAID drug is indicated, the lowest possible dosage must be selected. Should analgesics be needed, use of paracetamol/acetaminophen is recommended.

²⁵ Global Protocol Amendment 5 added “study outcome events” to this sentence.

²⁶ The last 2 paragraphs in this section were added with global Protocol Amendment 5.

6.9.2 Guidance for management of participants who have atrial fibrillation identified during study - amended

If a patient is diagnosed with AF during the study that requires oral anticoagulation according to the investigator's judgment, the patient will stop double-blind study medication. Per protocol, study medication must be permanently discontinued if AF is seen in a 12-lead ECG or if an AF episode of ≥ 6 minutes is identified during cardiac monitoring.²⁷ The patient will be offered open-label rivaroxaban according to the local label (if acceptable by local regulations) or alternatively, the investigator may prescribe other standard of care e.g., VKA. If the patient is switched to a VKA, adequate anticoagulation during the initiation phase needs to be ensured according to the Xarelto[®] Summary of Product Characteristics, due to the length of time required to achieve therapeutic anticoagulation with VKAs.

Patients receiving open-label rivaroxaban will continue with the regular study visits. For patients treated differently, the instructions for permanent discontinuation of study medication as outlined in Section 5.2 should be followed.

6.9.3 Guidance for management of participants who have coronary artery disease identified during the study

Patients diagnosed with coronary artery disease (CAD) during the study and in whom treatment with dual antiplatelet therapy is warranted (e.g., after percutaneous coronary intervention [PCI]) will interrupt study medication for the duration of dual antiplatelet therapy, as the combination of dual antiplatelet therapy and rivaroxaban 15 mg may lead to an increased bleeding risk. Study medication will be restarted once dual antiplatelet therapy is stopped.

For patients in whom treatment with ASA is recommended (e.g., stable CAD) the investigator can consider continuing study medication with non-study ASA only if the dose of ASA is ≤ 100 mg daily. Use of higher doses of ASA will require interruption of study medication.

6.9.4 Guidance for management of participants who have a recurrent ischemic stroke during the study

For patients who have a recurrent ischemic stroke during the study, a complete diagnostic work-up including brain imaging, at least 24-hour cardiac rhythm monitoring, and echocardiography is encouraged. All available clinically-obtained diagnostic results will be recorded on eCRFs for the purposes of event adjudication and secondary analyses.

No high-quality data are available regarding the use of intravenous thrombolysis for acute stroke in patients receiving rivaroxaban; therefore, the use of thrombolytic agents will follow local practice.

Based on the half-life of rivaroxaban of 11-13 hours in elderly patients, it may be anticipated that little or no drug is present in circulation, if the last dose of study medication was given at least 48 hours before. The anti-Factor Xa chromogenic assay, when used with validated calibrators and controls and where available, may be used to confirm that little or no residual

²⁷ This sentence was modified with global Protocol Amendment 5. See Section 13.1 for details.

anticoagulant effect is present. In addition, a normal prothrombin time (PT) value (measured using a rivaroxaban-sensitive reagent) suggests there is no clinically relevant anticoagulant effect of rivaroxaban.

As there is no contraindication for use of intravenous thrombolysis in patients with acute ischemic stroke who are receiving ASA, the treatment assignment can be emergently unblinded to facilitate decisions regarding intravenous thrombolysis.

Mechanical clot removal may be performed in any case.

6.9.5 Guidance for management of participants who have bleeding during the study

If a patient has serious bleeding during study treatment, the following routine measures could be considered:

- Delay the next study medication administration or discontinue study medication, if indicated
- Consider usual supportive treatment for bleeding, including local control of bleeding (if possible), fluid replacement, and blood transfusion

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

- Prothrombin complex concentrate (PCC)
- Activated prothrombin complex concentrate (APCC)
- Recombinant Factor VIIa

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Due to the high plasma protein binding, rivaroxaban is not expected to be dialysable.

6.9.6 Guidance for management of participants with overdose

Due to limited absorption, a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific antidote is not available. The use of activated charcoal to reduce absorption may be considered.

7. Procedures and variables

7.1 Schedule of procedures

As this is an event-driven study, patients will have different numbers of study visits. Patients will visit the clinic at screening, randomization, 1, 6, and 12 months and then every 6 months until the end of the study. At 3 months after randomization, the patient will be contacted by telephone. Patients will come to the clinic for an EOT visit followed by a telephone contact (Safety Visit) 1 month later.

7.1.1 Tabulated overview

A tabulated overview of the procedures conducted in this study is provided in the Table of procedures, provided at the end of the Synopsis.

7.1.2 Timing of assessments

7.1.2.1 Visit 1 (screening) - amended

Visit 1 will be used to assess the eligibility of the patient. After obtaining signed informed consent, the investigator will review the diagnostic tests required to diagnose ESUS. All diagnostic assessments for ESUS should be completed before the screening visit. If prolonged cardiac rhythm monitoring and/or echocardiography are not performed at time of screening, this can be done during the screening period. All acute therapies for stroke (e.g., thrombolysis) and diagnostic tests performed to diagnose acute stroke and ESUS will be recorded in the eCRF.²⁸

Demographic data (age, gender, race/ethnicity), weight (kg), height (cm), and medical history including reporting of stroke risk factors will be recorded at this visit. Laboratory assessments will include creatinine and eGFR (if not conducted at local laboratory within 1 month before screening, use value for eGFR as reported on laboratory report, otherwise calculate eGFR using MDRD formula, for which a calculator can be found for example on the internet www.mdrd.com) and pregnancy testing (only in women of childbearing potential). The modified Rankin score will be assessed as part of the exclusion criteria and NIHSS as part of the inclusion criteria.

The screening period will be 6 weeks maximum.²⁹

7.1.2.2 Visit 2 (randomization visit) - amended

Once all inclusion/exclusion criteria are fulfilled the patient will be randomized by accessing the IxRS system. The study medication will be assigned, and the patient will receive the study medication and instructions for its administration. The first dose of study medication can be given at this visit or at the time the patient will usually take study medication (same day or next day).

During this visit, study procedures will include the recording of ConMeds (Section 6.9) and vital signs (blood pressure [millimeters of mercury; mmHg] and heart rate [beats per minute; bpm]). Outcomes research questionnaires (Section 7.6.1) will be completed by the patient:³⁰

- European Quality of Life-5 Dimensions (EQ-5D) Questionnaire
- Montreal Cognitive Assessment (MoCA)
- Standard Assessment of Global-Activities in the Elderly (SAGE) questionnaire

²⁸ This paragraph was revised with global Protocol Amendment 5. See Section 13.1 for details.

²⁹ This sentence was added with global Protocol Amendment 5.

³⁰ The DSS test was removed with global Protocol Amendment 5 because implementation is not feasible due to a missing license.

Procedures for Visits 1 and 2 may be combined and performed at the same visit, if all eligibility criteria can be assessed at Visit 1 and no additional assessments are required before randomization (e.g., eGFR).

7.1.2.3 Regular study visits (visits 3 and onward) - amended

Patients will return to the study clinic at 1 month, 6 months, and then every 6 months. Patients who are at a rehabilitation or other clinic at the time of the 1 month visit (Visit 3), more flexibility will be allowed and this visit can be performed as a phone call instead of an onsite visit.³¹ At 3 months, the patient will receive a telephone call to obtain safety and outcome data and reinforce adherence to study medication and to avoiding non-study ASA.

The patient will be instructed to report any hospitalization or other significant illness to the investigator on an ongoing basis in order to allow a timely reporting of study outcomes and SAEs. In addition, at all visits, the patient will be specifically asked about potential study outcomes and AEs. If a suspected study outcome is reported, the respective eCRF will be completed and an adjudication package expeditiously compiled and submitted.

Vital signs will be collected at 6 months, 1 year, and then yearly thereafter.

Concomitant medications and weight will be collected once per year. If an SAE or study outcome event is reported, the use of any additional ConMeds should be recorded at that time.³²

The outcomes research questionnaires (MoCA and SAGE)³³ will be completed by the patient at the 1 year visit only. The EQ-5D will be completed every 6 months.

If a recurrent stroke is reported, the modified Rankin Score is to be assessed at 7 days post stroke or at hospital discharge, if this occurs before 7 days, and again at 3-6 months post stroke.³⁴ The modified Rankin score is also to be recorded at 1 year after stroke.

Study medication will be dispensed and returned every 6 months and study drug accountability and compliance will be recorded at these visits.

7.1.2.4 End of treatment (EOT) visit - amended

Within the trial close-out window prior to the end of the study (efficacy cut-off date), all patients must return to the clinic within 6 weeks in order to make a final assessment. In addition, for patients that permanently discontinued study medication and when further follow-up will no longer be done by site visits and rather by phone or third party contact, the patient will be encouraged to come for the EOT visit as soon as possible after discontinuation of study medication. For these patients a final vital status and outcome events will be collected during the trial close-out window. At this EOT visit, study procedures will include the collection of efficacy and safety outcome data, (S)AEs, vital signs, ConMeds, EQ-5D,

³¹ Sentence was added with global Protocol Amendment 5 to allow flexibility for patients after a stroke.

³² Global Protocol Amendment 5 added "or study outcome event" to this sentence for clarification.

³³ The DSS test was removed with global Protocol Amendment 5 because implementation is not feasible due to a missing license.

³⁴ The 3-month time point was expanded to 3-6 months with global Protocol Amendment 5 to allow flexibility and avoid additional visits.

MoCA, and SAGE questionnaires, and modified Rankin score. In addition, the study staff will collect the patient's empty and unused study medication bottles to allow final drug accountability and compliance checks.³⁵

Study medication 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.

7.1.2.5 Safety visit

Patients will be contacted by **telephone** 1 month after the last study medication intake to allow the collection of safety data.

7.2 Population characteristics

7.2.1 Demographics

Demographics include age, gender, race/ethnicity

7.2.2 Medical history

Medical history findings (i.e., previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the informed consent form (ICF)
- Considered relevant to the study

Medical history parameters to be collected at screening will include:

- Disease history associated with cerebro- and cardiovascular diseases and risk factors (stroke, transient ischemic attack, MI, angina pectoris, heart failure, peripheral artery disease, diabetes, hypertension, tobacco use)
- Surgical history (cerebro- and cardiovascular revascularizations)
- Other relevant diseases (renal dysfunction, liver disease, cancer, bleeding requiring transfusion)

7.3 Efficacy

7.3.1 Assessments and procedures at occurrence of efficacy outcome events

The analysis of efficacy outcome events will be based on events as adjudicated by the ICAC.

Occurrence of outcomes must be reported within 3 days of the site's notification of the event. Patients are requested to inform the site as soon as possible if they are hospitalized (regardless of reason) in order to ensure timely identification of potential CV events.

³⁵ This paragraph was amended with global Protocol Amendment 5. See Section 13.1 for details.

The following events will be reported on Outcome/CV Event reporting forms and will undergo adjudication by the ICAC:

- All deaths
- Stroke (ischemic, hemorrhagic or undetermined) and TIA
- Systemic embolism
- MI and hospitalization for cardiac chest pain

These events are exempted from SAE reporting with the exception of non-CV deaths.

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

7.3.2 Definition of efficacy outcome events

The following efficacy outcome events will be assessed and are defined in the following subsections of this protocol:

- stroke (Section 7.3.2.1)
- systemic embolism (Section 7.3.2.2)
- MI (Section 7.3.2.3)
- CV death (Section 7.3.2.4)
- all-cause mortality (Section 7.3.2.5)

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

7.3.2.1 Stroke

Stroke is 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 <24 hours, stroke requires neuroimaging evidence of acute brain ischemia (i.e. TIA with positive neuroimaging).

7.3.2.2 Systemic embolism

Systemic embolism is defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms.

7.3.2.3 Myocardial infarction

The term acute MI is used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. The diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The MI Universal Definition from 2012 (28) describes 5 types of myocardial infarction:

- Type 1 Spontaneous myocardial infarction
- Type 2 MI secondary to an ischemic imbalance
- Type 3 MI resulting in death when biomarker values are unavailable
- Type 4a MI related to percutaneous coronary intervention (PCI)
- Type 4b MI related to stent thrombosis
- Type 5 MI related to coronary artery bypass grafting (CABG)

7.3.2.4 Cardiovascular death

Cardiovascular death includes death due to stroke, myocardial infarction, heart failure or cardiogenic shock, sudden death or any other death due to other cardiovascular causes. In addition, death due to hemorrhage will be included.

7.3.2.5 All-cause mortality

All-cause mortality includes all deaths.

7.3.3 Efficacy variables

7.3.3.1 Primary efficacy variable

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

- Stroke (ischemic, hemorrhagic, and undefined stroke, TIA with positive neuroimaging)
- Systemic embolism

7.3.3.2 Secondary efficacy variables

The secondary efficacy variables of this study are the time from randomization to first occurrence of:

- Cardiovascular death (including death due to hemorrhage), recurrent stroke, systemic embolism, and MI
- All-cause mortality
- Individual components of the primary and secondary efficacy outcomes (stroke, CV death, and MI) as well as ischemic stroke, and disabling stroke (modified Rankin score 4 and 5)

7.4 Pharmacokinetics/pharmacodynamics

Not applicable.

7.5 Safety

The safety outcomes are bleeding events using the International Society on Thrombosis and Haemostasis (ISTH) major bleeding definition (29), and other definitions derived from these as listed in Section 7.5.1 and Section 7.5.2. Bleeding events will be reported on the bleeding reporting forms and exempted from SAE reporting. Potential major bleeding will undergo adjudication.

Information on bleeding will be collected in a way to also allow additional analysis using different bleeding definitions, e.g., Thrombolysis In Myocardial Infarction (TIMI) major bleeding and Global Use of Strategies to Open Occluded Arteries (GUSTO) severe/life-threatening bleeding. The analysis will be defined in the statistical analysis plan (SAP).

7.5.1 Primary safety variable - amended

The primary safety variable is the time from randomization to time of first occurrence of a major bleeding defined as a bleeding event that meets at least one of the following criteria:

- Fatal bleeding, and/or
- Symptomatic³⁶ bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), and/or
- Clinically overt bleeding associated with a recent decrease in the hemoglobin level of ≥ 2 g/dL³⁷ (20 g/L; 1.24 mmol/L) compared to the most recent hemoglobin value available before the event, and/or
- Clinically overt bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood

7.5.2 Secondary safety variables

The secondary safety variables are the time from randomization to time of first occurrence of:

- Life-threatening bleeding, defined as a subset of major bleeding that meet at least one of the following criteria:
 - Fatal bleeding
 - Symptomatic intracranial bleeding
 - Reduction in hemoglobin of at least 5 g/dl (50 g/l; 3.10 mmol/L)
 - Transfusion of at least 4 units of packed red cells or whole blood

³⁶ “Symptomatic” was added with global Protocol Amendment 5 in order to be consistent with the ISTH definition.

³⁷ Typographical error corrected with global Protocol Amendment 5 (more than 2 g/dL corrected to ≥ 2 g/dL).

- Associated with hypotension requiring the use of intravenous inotropic agents
- Necessitated surgical intervention
- Clinically relevant non-major bleeding, defined as non-major overt bleeding but
 - Requires medical attention (e.g., hospitalization, medical treatment for bleeding), and/or
 - Is associated with a study drug interruption of more than 14 days.
- Intracranial hemorrhage

7.5.3 Adverse events

7.5.3.1 Definitions

An **adverse event** (AE) is any untoward medical occurrence including an exacerbation of a pre-existing condition or abnormal laboratory finding in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE is considered serious (SAE) if it fulfills one or more of the following criteria:

- Results in death
- Is life-threatening
- Requires or prolongs hospitalization
- Is a congenital anomaly or birth defect
- Is a persistent or significant disability/incapacity
- Is another important medical event

Important medical event: Any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Important medical events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

Hospitalizations, which were planned before inclusion in the study (e.g., elective or scheduled surgery or other interventions arranged prior to the start of the study), will not be regarded as SAEs. This pertains also to hospitalizations which are ambulant (<12 hours) or are part of the normal treatment or monitoring of the studied disease or another disease present before inclusion in the study and which are not due to a worsening of the disease.

When AEs are captured on the Adverse Event Report Form of the eCRF its seriousness, duration, relationship to study drug, action taken, and outcome must be addressed.

7.5.3.2 Adverse event reporting - amended

The **safety observation period** extends from the time the signed informed consent is obtained through the completion of the final study visit, 1 month post the EOT visit. In case

of permanent discontinuation of study medication, AEs other than outcome events must be reported up to 1 month after the last dose of study medication intake (Safety Visit).

All SAEs, all non-serious AEs leading to permanent discontinuation of study-drug treatment, and any non-serious AEs of particular concern to the investigator will be captured in the eCRF. Other non-serious AEs will not be collected due to the large available safety database for rivaroxaban.

The following detailed rules apply to AE and SAE handling:

- SAEs which are primary or secondary efficacy outcomes or appear indicative of an outcome event, e.g., TIA, MI or cardiac chest pain requiring hospitalization will be captured on an Outcome/CV Event page of the eCRF.
- All fatal events which are not considered cardiovascular deaths will be captured as outcomes (Death eCRF) but will also be reported to the sponsor's Pharmacovigilance (PV) Department in an expedited manner.
- All bleeding events including fatal bleeding will be captured in the eCRF (Bleeding page). Serious adverse events which are bleeding terms will not be reported to the sponsor's PV Department in an expedited manner. Symptomatic intracerebral /intraparenchymal hemorrhages as well as symptomatic subarachnoid hemorrhages will be captured as bleeding and as stroke. All subdural/epidural hematoma and asymptomatic intracranial bleeding are only reported as bleeding.³⁸
- All other events (including complications of efficacy or safety outcome events) that fulfill the seriousness criteria will be reported as SAEs in an expedited manner.
- All pregnancies in female study patients or in female partners of a male study patient will be reported as Pregnancy reports in an expedited manner.
- Non-serious AEs that have led to permanent study-drug discontinuation will be recorded on the AE page of the eCRF.
- Non-serious AEs which the investigator considers of particular concern will be recorded on the AE page of the eCRF. These may include events that are unexpected and/or reveal a pattern that is suggestive of a possible causal association or other non-serious events significant enough as to prompt the investigator to bring them to the attention of the sponsor.
- Out of the AEs reported to sponsor's PV Department, reportable events (i.e., SUSARs) will be unblinded and reported to the competent authorities and Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) according to legal requirements.
- In order to maintain the integrity of the study, SUSARs that derive from outcome events including complications of outcome events (e.g., those arising from lack of expected drug effect or from hemorrhagic events, whether or not fatal) will be exempted from unblinding during the course of the trial and from expedited reporting

³⁸ The last 2 sentences in this bullet were added with global Protocol Amendment 5 to provide additional guidance for documentation in the eCRF.

as SUSARs. However, cases including non CV deaths will be eligible for unblinding and SUSAR reporting.

If reported, SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

A schematic of the outcome and event collection and reporting process is provided in [Figure 7-1](#).

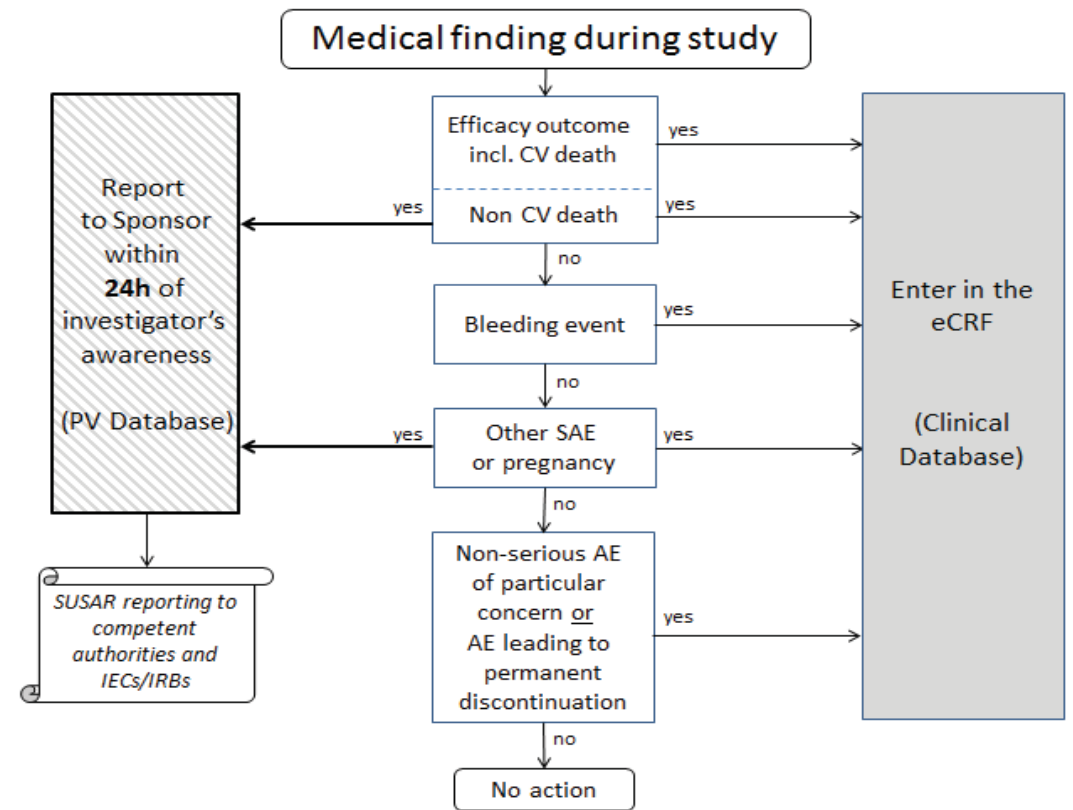


Figure 7-1: Outcome and adverse event collection and reporting schematic

The investigator must report immediately (within 24 hours of the investigator’s awareness) all SAEs described above as requiring expedited reporting to sponsor’s PV Department. The report recipients are detailed in the instructions for SAE reporting included in the Investigator File.

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.

7.5.3.3 Causal relationship of adverse events to study drug

The assessment of the causal relationship between an AE and the use of study drug is a clinical decision made by the investigator, who is a qualified physician, based on all available information at the time of the completion of the eCRF. The assessment is based on the question whether or not there was a "reasonable possibility" that the study drug caused the event. Possible answers are "yes" or "no".

An assessment of *no* would include the existence of a clear alternative explanation. Other reason for an assessment of *no* may be lack of 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 developing a few days after the first drug administration.

An assessment of *yes* indicates that there is a reasonable suspicion that the AE is associated with the use of the study drug. Factors in assessing the relationship of the AE to study drug include the temporal sequence from drug administration (the event should occur after the drug is given) and the length of time from drug exposure to event should be evaluated in the clinical context of the event. Furthermore, recovery on drug discontinuation (de-challenge), and recurrence on drug re-introduction (re-challenge, if available), underlying, concomitant, or intercurrent diseases should be evaluated in the context of the natural history and course of the disease being treated. In addition, concomitant medication or treatment, the pharmacology and pharmacokinetics of study drug should be considered.

7.5.3.4 Intensity of an adverse event, action taken, and outcome - amended

The intensity of an AE is assessed as mild (usually transient in nature and generally not interfering with normal activities), moderate (sufficiently discomforting to interfere with normal activities), and severe (prevents normal activities).

Any action on study treatment to resolve the AE is to be documented as: study drug withdrawn, interrupted, dose not changed, not applicable, or unknown.³⁹ Other specific treatment of AEs will be documented as: none, remedial drug therapy or other. The outcome of the AE is to be documented as: recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal or unknown.

7.5.3.5 Pregnancy reports

For a study patient, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported. For the pregnancy of a partner of a male study patient, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent. For all pregnancy reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE, i.e., within 24 hours of his/her awareness.

³⁹ The options "dose reduced" and "dose increased" were removed with global Protocol Amendment 5 as they do not pertain to this study.

7.5.3.6 Expected adverse events

The expectedness of AEs will be determined by the sponsor according to the applicable reference document which for this study is the most current version of the investigator's brochure (IB)/company core data sheet. If new relevant safety information is identified, it will be integrated into an update of the IB and distributed.

Unexpected adverse events

An unexpected AE is any AE whose specificity or severity is not consistent with the IB or company core data sheet. Also, reports which add significant information on specificity or severity of an already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the investigator brochure would be considered "unexpected".

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. For handling different events classified as SUSARs see Section 7.5.3.2.

7.6 Other procedures and variables

7.6.1 Health Economics and Outcomes Research

Patients will be asked to complete a quality of life questionnaire, and 3 cognitive and functional assessment questionnaires during the study conduct.

7.6.1.1 Healthcare Resource Use

Health care resource utilization data related to all efficacy and safety outcomes events will be collected for all patients during the study. These will include: hospitalizations (total days length of stay, intensive care unit/cardiac care unit days, ward type); emergency room visits; unscheduled outpatient physician consultations; or visits related to bleeding, surgeries, other selected procedures (inpatient and outpatient); and post-stroke care (status of care, home health or rehabilitation center or long term care). Days off-work will also be documented. Only occurrence of these events (with identifying information such as types of procedures) will be collected. Country-specific cost data will be linked at a later stage.

7.6.1.2 European Quality of Life-5 Dimensions

A quality of life assessment tool, the European Quality of Life-5 Dimensions Questionnaire (EQ-5D) will be administered at Day 0 (randomization), every 6 months, and at the EOT visits. This is a standardized instrument for use as a measure of health outcomes. The assessment is 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.

7.6.1.3 Montreal Cognitive Assessment and Standard Assessment of Global-Activities in the Elderly - amended

⁴⁰The MoCA will be included in the study to assess cognition and the SAGE questionnaire will be used to assess functional outcome. These tests and questionnaires will be administered at Day 0 (randomization), 1 year, and at the EOT visits. The patients will be asked to independently complete the MoCA test to the best of their ability. Otherwise, the reason for not completing must be documented. The SAGE questionnaire may be completed with the help of the study staff.

7.6.1.4 Modified Rankin Score - amended

In addition to the regular assessments at screening, 1 year, and EOT, the Modified Rankin Score will be assessed by the investigator at 7 days or at discharge, if this occurs before 7 days, and again at 3-6 months⁴¹ after a recurrent stroke. The scale spans 0-6, perfect health without symptoms to death.

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 - Dead.

8. Statistical methods and determination of sample size

8.1 General considerations

A general description of the statistical methods is outlined below. An SAP will be provided in a separate document and will contain a more technical and detailed description of the principal features of the planned analyses, e.g., censoring schemes for time-to-event variables.

The core SAP will be finalized prior to study enrollment. Amendments and/or appendices to the core SAP will provide more details on the coding guidelines, data-handling, and output tables and figures. These SAP associated documents are targeted for completion 6 months

⁴⁰ The DSS test was deleted with global Protocol Amendment 5 because implementation is not feasible due to missing license.

⁴¹ The 3-month time point was expanded to 3-6 months with global Protocol Amendment 5 to allow flexibility and avoid additional visits.

before planned study end to take into account emerging data external to the trial that could influence study interpretation. All SAP associated documents will be finalized without knowledge of any emerging results from the trial.

Analyses will be performed using SAS software (SAS Institute Inc., Cary, NC, USA).

8.2 Analysis sets

8.2.1 Efficacy data set

The efficacy analysis will be based on the ITT population, which comprises all randomized patients. In the International Conference on Harmonisation (ICH) E9 guideline this is also termed the full analysis set, FAS. Patients will be categorized to the group to which they were assigned by the IxRS.

8.2.2 Safety data set

The safety analysis will be based upon the safety data set (SAF) which will comprise 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.

8.2.3 Data scopes

The following data scopes will be defined for efficacy and safety analyses.

Data scope according to intention-to-treat principle

The ITT data scope includes 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. This will be the primary data scope for the efficacy analyses.

Data scope according to treatment

The on-treatment data scope will include all outcome events observed from randomization until 2 days following permanent discontinuation of the study drug.

8.3 Variables

The efficacy variables are defined in Sections [7.3.3.1](#) and [7.3.3.2](#).

The safety variables are defined in Sections [7.5.1](#) and [7.5.2](#).

8.3.1 Subgroup variables

The following subgroup analyses based on baseline demographics are planned:

- Age: <60; 60-75; >75 age
- Sex: male; female
- Race: White; Black; Asian; other
- Region: North America; South America; Western Europe; Eastern Europe; Asia

- BMI: < 25; ≥ 25 to < 30; ≥ 30kg/m²
- Weight: <70; 70-90; >90 kg
- eGFR: <50; 50-80; >80 mL/min
- Stroke or TIA prior to index event: yes or no
- Time from index stroke to randomization: ≤30 days; 30 days to 3 months; > 3months
- Presence of patent foramen ovale: present or absent / not known
- Cardiac rhythm monitoring: <48; ≥ 48 hours
- Hypertension: yes or no
- Diabetes: yes or no

Even though rivaroxaban has not been tested in patients with ESUS, based on earlier studies with rivaroxaban a consistent (relative) treatment effect across all of the planned subgroups is expected. However, higher efficacy event rates are expected for the following subgroups: older age, females, renal impairment, stroke or TIA prior to index event, hypertension, and diabetes.

8.4 Statistical and analytical plans

Summaries by treatment group using appropriate descriptive statistics will be provided for all study variables including demographic and baseline characteristics. Mean, median, standard deviation, minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables.

8.4.1 Analysis of the primary efficacy variable

In order to evaluate whether rivaroxaban is superior to ASA in prolonging the time to a primary efficacy outcome event in patients with ESUS, the following null hypothesis (H) will be tested at the significance level of 0.025:

$H_{0, PE}: S_R(t) = S_A(t)$ for all time points $t \geq 0$, (i.e. “there is no difference between the rivaroxaban treatment group and the ASA control group regarding the primary efficacy outcome for all time points”)

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 and S_A denotes the survival function of the ASA group.

The following decision rule to test the null hypothesis will be applied:

According to the size of this study, it is justified to assume under $H_{0, PE}$ a sufficiently close approximation of the one-sided stratified (according to age) log-rank test to the normal distribution. If the z-value from the one-sided log-rank test (for the difference

$S_R(t) - S_A(t)$ with stratification⁴²) is larger than the critical quantile from the normal distribution ($z_{0.975} = 1.96$), the null hypothesis will be rejected in favor of the alternative hypothesis.

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.

Hazard ratio, relative risk reduction, and corresponding two-sided 95% confidence intervals will be estimated based on an age-group stratified Cox proportional hazards models. 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. Censoring will be assumed independent of the treatment group assignment.

Further details will be specified in SAP.

8.4.2 Analysis of secondary efficacy variables

The secondary efficacy outcomes will be ordered and tested in a sequential manner as listed in Section 7.3.3.2

If the superiority of rivaroxaban for the primary outcome is declared, the following alternative hypotheses, superiority of rivaroxaban compared with ASA for the secondary efficacy outcomes will be tested in the sequential order. That is, the subsequent ordered secondary outcome will be tested only if superiority can be shown for the previous outcomes. If an individual test during any step is not statistically significant, further testing may continue but significance will not be claimed. This hierarchical testing procedure will control the global Type 1 error level.

The analysis methods will be similar to those described for the primary efficacy outcome.

8.4.3 Analysis of safety variables

The analysis methods will be similar to those described for the primary efficacy outcome.

8.4.4 Subgroup analysis

Subgroup analyses for the primary efficacy and safety outcomes will be performed based on the same analysis sets and data scopes as in the main analyses of the study outcomes. The subgroup analyses will be presented descriptively without formal hypotheses testing.

Homogeneity of treatment effect in subgroups, both in magnitude and direction, will be assessed by adding a covariate for the subgroup variable and the corresponding treatment-subgroup interaction to the respective Cox proportional hazards model used in the main analysis. Additionally the hazard ratio for the treatment effect will be estimated separately within each level of a subgroup variable using the same Cox proportional hazards. As the number of subgroup analyses may be large, the probability of observing at least one

⁴² Typographical error was corrected with global Protocol Amendment 5 (“without stratification” was corrected to “with stratification”).

spurious interaction is high despite the lack of a biological or pharmacological basis for expecting an interaction. Thus, any interactions with a p-value below the 5% type I error level in the analysis of primary outcomes will be interpreted as “flags” to prompt further investigation. This further investigation includes the likelihood ratio test proposed by Gail and Simon to test for qualitative interaction.

8.4.5 Handling of missing data

All efforts will be made to collect complete data for all patients randomized in this study. 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 known, the site investigator will be asked to provide a best estimate as to when the event occurred. Even though the exact date of an event is unknown, the investigator often does know some information that would indicate the approximate date, such as the first week of a month, in the fall of a year, or the middle of a particular year, or at least the date when the patient was last seen or contacted. This information can be meaningfully incorporated into the estimated date recorded, as this is likely to be closer to the true date than any produced by an uninformed computer program. This estimated date should be the middle date within the period that the event is known to have occurred. If the event is known to have occurred in the first week of a month, then the date in the middle of that week should be recorded as the estimate. If it occurred in the fall of a year, then the middle date in the fall is the appropriate estimate. If no information is known then the date in the middle of the plausible time period should be given, based on the last contact with the patient prior to the event and the date of contact when information about the event was known.

8.5 Planned interim analyses - amended

⁴³The IDMC will monitor the study for greater than expected efficacy and for safety. There will be 2 formal interim analyses to assess efficacy, which will occur when approximately 50% and 67% of the planned primary efficacy events have accrued. The IDMC may recommend early study termination at these interim analyses, if there is overwhelming superiority of rivaroxaban ($Z > 4$) for efficacy. 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 over ASA.

The IDMC has the flexibility to initiate further interim analyses after the first formal efficacy analysis at 50%, if deemed appropriate. Given the conservative nature of the monitoring guidelines used in the trial, no adjustment of the significance level for the final analysis is required.

The execution of the interim analyses and decision rules will be specified in the IDMC charter.

8.6 Determination of sample size - amended

The study is event-driven and it is estimated that 7000 patients (3500 per treatment group) need to be randomized in order to have approximately 450 patients experiencing a confirmed primary efficacy outcome event. This number of events will allow the demonstration of superiority of rivaroxaban compared to ASA with regard to the primary outcome with a power of 90% and a one-sided level of significance $\alpha = 0.025$ under the following assumptions:

- An average yearly event rate of the composite primary efficacy outcome of 3.8% in the ASA group (4.0% for patients with age ≥ 60 years, 2.0% for 10% of patients with age < 60 years)
- A 30% RRR for stroke and systemic embolism in the rivaroxaban group compared to ASA
- Approximately 10% of patients will permanently discontinue study medication in the first year and 7% in following years
- Approximately 5% of patients with a diagnosis of AF will switch to standard treatment during study conduct
- Approximately 3% patient deaths per year and 1% of patients lost to follow-up per year

Under these assumptions the expected RRR to be observed in this study would be 26% for the primary efficacy outcome.

⁴³ Global Protocol Amendment 5 added an interim analysis and changed the criteria and approach for assessing overwhelming superiority of rivaroxaban. Details of the interim analyses will no longer be specified in the SAP, but in the IDMC charter only. The second paragraph was also added.

The number of patients enrolled in the total study may be adjusted or enrollment in the age group 50-59 years may be stopped based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study.⁴⁴

9. Data handling and quality assurance

9.1 Data recording - amended

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the site. The site must implement processes to ensure this happens. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

Data recorded from “only screened patients (screening failures)”

Data of 'only screened patients' will be recorded as source data, as far as the reason for not randomizing the patient into the study is identifiable. At minimum, data to be recorded in the eCRF are demographic information (patient number, date of birth/age, sex, race and ethnicity), the reason for screening failure and date of last visit.⁴⁵ These data will be transferred to the respective database.

For screening failures with an SAE, the following additional data should be collected in the eCRF, in addition to demographic information, primary reason for discontinuation and date of last visit:

- All information about the SAE
- All information related to the SAE such as:
 - concomitant medications
 - medical history
 - other information needed for SAE complementary page

9.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's (contract research organization'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.

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

⁴⁴ Sentence revised with global Protocol Amendment 5. See Section 13.1 for details.

⁴⁵ The first 2 sentences of this paragraph were revised for clarification with global Protocol Amendment 5. See Section 13.1 for details.

- 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.

9.3 Data processing

The data collection tool for this study will be a validated electronic system called iDataFax. Patient data necessary for analysis and reporting will be transmitted into a validated database or data system (e.g., TOSCA; SAS). Clinical data management will be performed in accordance with agreed standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g., IxRS, adjudication committees).

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

9.4 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.

9.5 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.

10. Premature termination of the study

The sponsor has the right to close this study or centers at any time, which may be due but not limited to the following reason:

- If risk-benefit ratio becomes unacceptable owing to, for example,
 - Safety findings from this study (e.g., SAEs)
 - Results of the review by the IDMC
 - Results of parallel clinical studies

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.

Closures should occur only after consultation between involved parties and all affected institutions must be informed as applicable according to local law.

Details for individual patient's discontinuation of study medication and withdrawal of consent can be found in Section 5.2.

11. Ethical and legal aspects

11.1 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 GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IECs/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 IEC/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 10.

11.2 Subject information and consent

All relevant information on the study will be summarized in integrated patient information sheets and ICFs, provided by the sponsor. Sample patient information sheets and ICFs are provided as a document separate to this protocol.

Based on the patient information sheet for the respective study phase, the investigator or designee will explain all relevant aspects of the study to each patient/legal representative or proxy consentor (if the patient is under legal protection), 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 IEC/IRB has been obtained.

Each patient/legal representative or proxy consentor will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the patient/legal representative or proxy consentor voluntarily agrees to sign the ICF and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The patient/legal representative or proxy consentor 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/legal representatives or proxy consentors 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/legal representative or proxy consentor 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.

11.3 Publication policy

The study results will be reported irrespective of the outcome of the study. The SC will decide on the authorship of all papers. The main study results will be written by a writing group lead by members of the SC on behalf of the whole study group, and may include additional individuals who have made substantial and sustained contributions.

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

11.4 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.

11.5 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 or documents sent for adjudication of outcome events), 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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13. Protocol amendments

13.1 Amendment 5

13.1.1 Overview of changes to the study

The following modifications are introduced in Protocol Version 2.0:

1. The following eligibility criteria were revised (the synopsis, Figure 4-1, Sections 4.1, 5.1.1, 5.1.2, and 6.3 were updated):
 - More details have been provided in the definition of a lacunar stroke in order to avoid protocol deviations.
 - Due to the approximation of the reporting of cervical carotid atherosclerotic stenosis, subjects will be included if there is no stenosis > 50% rather than $\geq 50\%$ to prevent eligible patients from being excluded. Likewise, they will be excluded if there is an intracranial stenosis > 50%.
 - For patients with intracranial arterial occlusions in the territory of the qualifying stroke, it was clarified that a patient is eligible if the investigator believes the occlusion is due to embolism, and not atherosclerotic based on absence of intracranial atherosclerosis elsewhere.
 - For the 24-hour cardiac rhythm monitoring assessment to exclude the presence of AF, an allowance was added to accept a 20-hour recording to reflect routine practice.
 - For the determination of intra-cardiac thrombus, the allowance of transesophageal echocardiography was added as well as transthoracic echocardiography.

The recruitment of patients was changed from *18 years of age or older* to *50 years of age or older* because this will only allow inclusion of patients with a high risk for a recurrent stroke.

Additional clarifications were made to the to the inclusion criterion regarding the patients enrolled with certain risk factors:

- Clarification that covert/silent strokes on neuroimaging and current tobacco smoker count as risk factors.
- Clarification that each risk factor counts separately (ie, “*stroke or TIA prior to index stroke, diabetes, hypertension, and heart failure*” changed to “*stroke or TIA prior to index stroke [includes covert/silent strokes on neuroimaging], diabetes, hypertension, current tobacco smoker, or heart failure*”)
- The rate of recurrent stroke is not known for ESUS patients between ages 50 and 59 who also have additional risk factors and cannot be reliably estimated from available data. Therefore, the age restriction has changed from < 60 years of age with a cap at 10% of the total study population to ≥ 50 years and requirement for an additional risk factor for patients between 50-59 years. Also, clinicians want

to know whether to anticoagulate the substantial fraction of ESUS patients who are under 60 years of age. NAVIGATE ESUS as originally designed (ie, the 10% recruitment cap) would not provide sufficient data to address this question meaningfully.

Clarification was made to the bleeding exclusion criterion 9.

2. The number of patients enrolled in the total study may be adjusted or enrollment in the age group 50-59 years may be stopped based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study. The synopsis (Number of subjects) and Section 8.6 were revised.
3. To allow flexibility, changed that all diagnostic assessments for ESUS *must* be completed before the screening visit to *should* be completed before the screening visit. If prolonged cardiac rhythm monitoring and/or echocardiography are not performed by the time of screening, these assessments can be done during the screening period. The screening period was extended from 4 weeks to 6 weeks (maximum) to allow for this. The Table of procedures and Section 7.1.2.1 were revised.
4. The DSS testing requirement was removed. Due to a missing license, the implementation of this test is not feasible. The Table of procedures and Sections 7.1.2.2, 7.1.2.3, 7.1.2.4, 7.6.1.3, and 14.1.1 were updated.
5. Clarifications were made to avoid misunderstanding regarding the required assessments at EOT. The Table of procedures and 7.1.2.4 were revised.
6. In order to allow more flexibility for patients who are at a rehabilitation clinic after a stroke at the time of Visit 3, a phone call may replace the onsite visit. The Table of procedures and Section 7.1.2.3 (it was also clarified that if a study outcome event is reported ConMeds should be reported) were revised.
7. Corrections were made to data from the PICSS study in Section 1.3.
8. The number of participating countries was updated in Section 5.
9. In Section 5.2, it was clarified that in case a patient is diagnosed with atrial fibrillation with an episode of ≥ 6 minutes during the study, trial medication must be stopped and that a temporary study medication is a “interruption” and not a “discontinuation.” Also, a sentence that stated that patients who permanently discontinue the study will not be reactivated was deleted because this point is covered by exclusion criterion 16 and the statement does not belong in this section.
10. Unblinding will be by a country toll-free help line only (no web-based unblindings). The possibility for treating physicians to unblind was added. Section 6.5.1 was updated.
11. Information about collecting drug interruption details relating to study outcome events was added to Section 6.7.
12. Additional information was provided in Section 6.9 regarding prohibited concomitant medications.

13. Clarification was added for diagnosing AF during the study. In addition to cardiac monitoring, a 12-lead ECG is permissible in lieu of a Holter or other prolonged monitoring method. Section 6.9.2 was revised.
14. The definition of major bleeding was revised for consistency with the ISTH definition. Section 7.5.1 was revised.
15. Additional guidance has been provided in Section 7.5.3.2 for the documentation of intracranial hemorrhage.
16. Dose increases and reductions are not applicable in this study, therefore these options were deleted from the list of choices for “study treatment action” due to AEs in Section 7.5.3.4.
17. The Modified Rankin Score assessment is required 3 months after a recurrent stroke. A range was added (3 to 6 months) to allow flexibility and avoid an additional site visit. The Table of procedures and Sections 7.1.2.3 and 7.6.1.4 were revised.
18. A second interim analysis has been added and the criteria and approach for assessing overwhelming superiority of rivaroxaban has changed as requested by the IDMC. An option to initiate further interim analyses after the first formal efficacy analysis at 50% was added. Details of the interim analyses will no longer be specified in the SAP, but in the IDMC charter only. The synopsis and Section 8.5 was revised.
19. Wording was clarified in Section 9.1 in order to avoid misunderstanding between “premature discontinuation” and “screening failure” and that source data should be documented.
20. The following revisions were made to the MRI substudy in Section 14.1.1:
 - The primary endpoint was changed to allow a more sensitive analysis for the entire study population. The secondary endpoint was updated accordingly.
 - For the baseline MRI, text pertaining to the timing was clarified. A provision was added for a repeat scan in the event the initial scan was not technically acceptable.
 - Further specification was made as to the timing of the follow-up MRI
21. Some typographical errors were corrected and minor editorial and formatting changes were made in Sections 5.1.1, 6.9.2, 7.5.1, 8.4.1, 12, and 14.

13.1.2 Changes to the protocol text

All sections of the protocol affected by the amendment are shown below. Deleted text is ~~crossed out~~ and added text is underlined. Corrections of typographical errors or editorial corrections are not highlighted.

Synopsis, Diagnosis and main criteria for inclusion

- Absence of cervical carotid atherosclerotic stenosis greater than ~~or equal to~~⁴⁶ 50% or occlusion, and

⁴⁶ Symbols are used in the text (ie, \geq and $>$)

- No atrial fibrillation after \geq 24-hour cardiac rhythm monitoring (at least 20 hours acceptable), and
- No intra-cardiac thrombus on either transesophageal or transthoracic echocardiography, and

Synopsis, Methodology

Patients who fulfill all inclusion and none of the exclusion criteria after giving informed consent will be randomly allocated 1:1 to either rivaroxaban 15 mg or aspirin 100 mg orally once daily. Randomization will be stratified by country and age <60 and ≥ 60 years. ~~No more than 10% of the total patient population will be randomized into the age group <60 years.~~

Synopsis, Number of subjects

The number of patients enrolled in the total study may be adjusted or enrollment in the age group 50-59 years may be stopped based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study.

Synopsis, Plan for statistical analysis

There will be ± 2 formal interim ~~analysis~~ analyses to assess efficacy and stop for overwhelming superiority, which will occur when approximately 50% and 67% of the planned primary efficacy outcomes have accrued.

Table of procedures

	Screen	Random	Treatment Phase						Washout
	V1	V2	V3	V4	V5	V6	V7-V [∞]	EOT ^a	Safety Visit
Timelines	-4-6 to 0 wks^b	0	1 Mo	3 Mo	6 Mo	12 Mo	every 6 Mo	End of Treat	1 Mo post EOT
Visit Window (weeks)			±1	±4	±4	±4	±4		±1
Type of Visit	Visit	Visit	Visit_L	☎	Visit	Visit	Visit	Visit	☎
.....									
EQ-5D MoCA, DSS, and SAGE		• •			•	•	•	•	

Abbreviations: EOT = end of treatment; Mo = month; V = visit, ☎ = telephone contact; eGFR = estimated glomerular filtration rate; ConMeds = Concomitant medications; MoCA = Montreal Cognitive Assessment; DSS = Digit Symbol Substitution test; SAGE = Standard Assessment of Global-Activities in the Elderly; EQ-5D = European Quality of Life-5 Dimensions questionnaire; SAE = serious adverse event; TIA = transient ischemic attack; MI = myocardial infarction

- a End of treatment visit is to be performed within the trial close-out window before the end of the study (efficacy cut-off date) or once the patient has permanently discontinued study medication and when no further visits at the site will be performed
- b Screening visit can be the same as randomization visit, if all required tests for eligibility criteria are available at screening visit. Maximum screening period -4-6 weeks.

.....

- k For definition see Section 7.6.1.4. In case of recurrent stroke to be done at 7 days post stroke or at discharge from hospital in case this occurs before 7 days and again at 3-6 months post stroke

L Patients who are at a rehabilitation or other clinic at the time of the 1 month visit (Visit 3), more flexibility will be allowed and this visit can be performed as a phone call instead of an onsite visit.

.....

Section 1.3 Studies assessing the efficacy of anticoagulation for secondary prevention of embolic stroke of undetermined source, last sentence of 3rd paragraph

In addition, in the PICSS study, ~~260~~ 98 participants with a patent foramen ovale, the primary outcome (2 year rate of recurrent ischemic stroke or death) was halved in those assigned to warfarin (9.5% warfarin vs. 17.9% ASA).

Section 4.1 Overview, 4th and 5th paragraphs

Patients will be ~~enrolled~~ randomized as early as possible after the required diagnostic evaluation is complete and eligibility criteria are fulfilled. The goal is that the majority of patients are enrolled within 3 months, and fewer patients between 3 and 6 months.

Randomization will be stratified by country and age <60 and ≥60 years. ~~No more than 10% of the total patient population will be randomized into the age group <60 years, as patients with <60 years have a lower risk for recurrent stroke.~~ Patients < 60 years will need to have at least one risk factor such as stroke (includes covert/silent strokes on neuroimaging) or TIA prior to index stroke, diabetes, hypertension, current tobacco smoker or and heart failure.

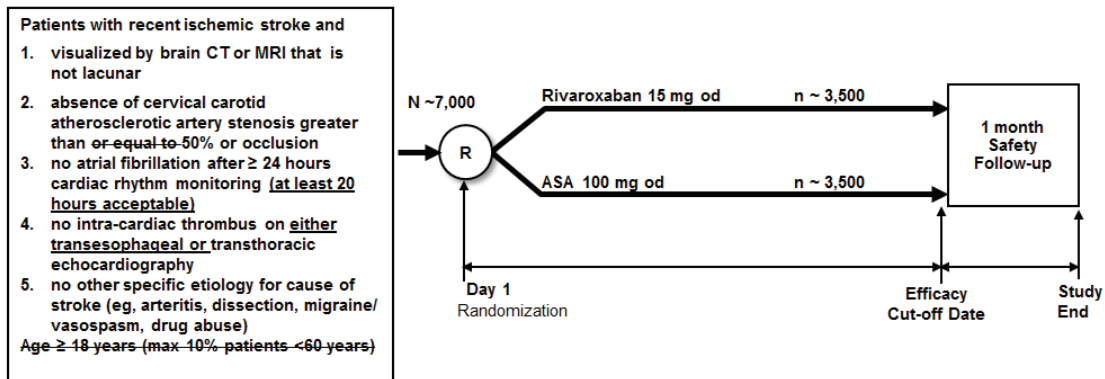


Figure 4-1

Section 5 Study population

This Phase III, multi-national, study will be conducted in ~~25 to 30~~ approximately 30 countries worldwide in approximately 7000 patients recruited primarily from hospital-based stroke units.

Section 5.1.1 Inclusion criteria

1. Embolic stroke of undetermined source (ESUS) defined as:
 - Recent ischemic stroke (including TIA with positive neuroimaging) visualized by brain CT or MRI that is not lacunar (i.e., lacunar infarcts are subcortical infarcts ≤ 1.5 cm in the territory of middle cerebral artery or pons; infarcts involving the cerebellum or lateral medulla are not considered as lacunar infarcts). Patients with multiple simultaneous acute lacunar infarcts on DWI imaging may be included. In case of embolic large artery occlusions clearly documented on angiography who undergo successful recanalization, visualization of infarct on neuroimaging is not mandated, and
 - Absence of cervical carotid atherosclerotic stenosis (or vertebral and basilar artery atherosclerotic stenosis in case of posterior circulation stroke), that is greater than ~~or equal to~~ ⁴⁷ 50%, or occlusion in arteries supplying the area of ischemia in CT or magnetic resonance (MR) angiography or conventional angiography or ultrasound, and
 - No history of AF, no documented AF on 12-lead electrocardiogram (ECG) or episode of AF lasting 6 minutes or longer detected after ≥ 24 -hour cardiac rhythm monitoring (Holter or telemetry; at least 20 hours acceptable), and
 - No intra-cardiac thrombus on either transesophageal or transthoracic echocardiography, and
 - ...

⁴⁷ Symbols are used in the text (ie, \geq and $>$)

4. Age ~~≥18~~ 50 years (~~or respective country specific legal lower age limit if this is >18 years~~)
5. For patients with age ~~<60~~ 50-59 years at least one of the following risk factors: stroke or TIA prior to index stroke (includes covert/silent strokes on neuroimaging), diabetes, hypertension, current tobacco smoker ~~and~~ or heart failure.

Section 5.1.2 Exclusion criteria

2. If imaging of intracranial arteries is performed by CT or MR angiography or transcranial Doppler: greater than ~~or equal to~~⁴⁸ 50% luminal stenosis or occlusion in arteries supplying the area of ischemia
9. Active bleeding, major bleeding within last 6 months, ~~history of primary intracranial hemorrhage~~ or high risk for serious bleeding contraindicating anticoagulant or antiplatelet therapy or history of primary intracranial hemorrhage

Section 5.2 Discontinuation of patients from study treatment, 2nd, 3rd, and 8th paragraphs

Patients may discontinue study medication at their own request and without giving reasons (even though providing a reason is encouraged), based on the investigator's judgment, if the patient is pregnant, or at the request of the sponsor (exceptional circumstances). In case a patient is diagnosed with atrial fibrillation with an episode of at least 6 minutes during the study trial medication must be stopped (see section 6.9.2)....

In case of a temporary study medication ~~discontinuation~~ interruption for any reason, study medication will be restarted as soon as medically justified in the opinion of the investigator. There is no defined maximum limit for temporary treatment interruption.

....

~~Patients who permanently discontinue the study for any reason will not be reactivated.~~

Section 6.3 Treatment assignment, sentence deleted

~~No more than 10% of the total patient number will be randomized into the age group < 60 years.~~

Section 6.5.1 Emergency unblinding by the investigator

Unnecessary unblinding should be avoided and should only be undertaken by the investigator or the treating physician when it is essential for the patient's safety. In such a situation, the investigator will be able to unblind the patient via the ~~IXRS system~~ country toll-free help line.

Section 6.7 Treatment compliance

First dose, last dose, and any dose interruptions of study medication due to AEs, study outcome events, or of >7 days for any other reason will be reported in the eCRF.

Section 6.9 Prior and concomitant therapy

⁴⁸ Symbols are used in the text (ie, ≥ and >)

No specific concomitant medications are prohibited other than strong inhibitors of both CYP3A4 and Pgp inhibitors. This includes human immunodeficiency virus protease inhibitors and the following azole antimycotics agents: ketoconazole, itraconazole, voriconazole, or posaconazole, if used systemically. However, fluconazole is allowed.

In addition, concomitant use with antiplatelets and anticoagulants is outlined in the sections below.

Section 6.9.2 Guidance for management of participants who have atrial fibrillation identified during the study

If a patient is diagnosed with AF during the study that requires oral anticoagulation according to the investigator's judgment, the patient will stop double blind study medication. Per protocol, study medication must be permanently discontinued if AF is seen in a 12-lead ECG or if an AF episode of greater than or equal⁴⁹ to 6 minutes is identified during cardiac monitoring.

Section 7.1.2.1 Visit 1 (screening)

Visit 1 will be used to assess the eligibility of the patient. After obtaining signed informed consent, the investigator will review the diagnostic tests required to diagnose ESUS. All diagnostic assessments for ESUS ~~must~~ should be completed before the screening visit. If prolonged cardiac rhythm monitoring and/or echocardiography are not performed at time of screening, this can be done during the screening period.

The screening period will be 6 weeks maximum.

Section 7.1.2.2 Visit 2 (randomization visit)

Outcomes research questionnaires (Section 7.6.1) will be completed by the patient:

- European Quality of Life-5 Dimensions (EQ-5D) Questionnaire
- Montreal Cognitive Assessment (MoCA)
- ~~Digit Symbol Substitution (DSS) test~~
- Standard Assessment of Global-Activities in the Elderly (SAGE) questionnaire

Section 7.1.2.3 Regular study visits (visits 3 and onward), 1st, 4th, 5th and 6th paragraphs

Patients will return to the study clinic at 1 month, 6 months, and then every 6 months. Patients who are at a rehabilitation or other clinic at the time of the 1 month visit (Visit 3), more flexibility will be allowed and this visit can be performed as a phone call instead of an onsite visit. At 3 months, the patient will receive a telephone call to obtain safety and outcome data and reinforce adherence to study medication and to avoiding non-study ASA.

...

Concomitant medications and weight will be collected once per year. If an SAE or study outcome event is reported, the use of any additional ConMeds should be recorded at that time

⁴⁹ Symbols are used in the text (ie, > and ≥).

The outcomes research questionnaires (MoCA, ~~DSS~~, and SAGE) will be completed by the patient at the 1 year visit only. The EQ-5D will be completed every 6 months.

If a recurrent stroke is reported, the modified Rankin Score is to be assessed at 7 days post stroke or at hospital discharge, if this occurs before 7 days, and again at 3-6 months post stroke. The modified Rankin score is also to be recorded at 1 year after stroke.

Section 7.1.2.4 End of treatment (EOT) visit

~~When the sponsor announces~~ Within the trial close-out window prior to the end of the study (efficacy cut-off date), all patients must return to the clinic within 6 weeks in order to make a final assessment. In addition, for patients that permanently discontinued study medication and when further follow-up will no longer be done by site visits and rather by phone or third party contact, the patient will be encouraged to come for the EOT visit as soon as possible after discontinuation of study medication. For these patients a final vital status and outcome events will be collected during the trial close-out window. At this EOT visit, study procedures will include the collection of efficacy and safety outcome data, (S)AEs, vital signs, ConMeds, EQ-5D, MoCA, ~~DSS~~ and SAGE questionnaires, and modified Rankin score. In addition, the study staff will collect the patient's empty and unused study medication bottles to allow final drug accountability and compliance checks.

Section 7.5.1 Primary safety variable

- Symptomatic bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), and/or

Section 7.5.3.2 Adverse event reporting, 3rd bullet

- All bleeding events including fatal bleeding will be captured in the eCRF (Bleeding page). Serious adverse events which are bleeding terms will not be reported to the sponsor's PV Department in an expedited manner. Symptomatic intracerebral/intraparenchymal hemorrhages as well as symptomatic subarachnoid hemorrhages will be captured as bleeding and as stroke. All subdural/epidural hematoma and asymptomatic intracranial bleeding are only reported as bleeding.

Section 7.5.3.4 Intensity of an adverse event, action taken, and outcome

Any action on study treatment to resolve the AE is to be documented as: study drug withdrawn, interrupted, ~~dose reduced~~, dose not changed, ~~dose increased~~, not applicable, or unknown.

Section 7.6.1.3 Montreal Cognitive Assessment, ~~Digit Symbol Substitution test~~, and Standard Assessment of Global-Activities in the Elderly

The MoCA ~~and DSS~~ will be included in the study to assess cognition and the SAGE questionnaire will be used to assess functional outcome. These tests and questionnaires will be administered at Day 0 (randomization), 1 year, and at the EOT visits. The patients will be asked to independently complete the MoCA ~~and DSS~~ tests to the best of their ability. Otherwise, the reason for not completing must be documented. The SAGE questionnaire may be completed with the help of the study staff.

Section 7.6.1.4 Modified Rankin Score

In addition to the regular assessments at screening, 1 year, and EOT, the Modified Rankin Score will be assessed by the investigator at 7 days or at discharge, if this occurs before 7 days, and again at 3-6 months after a recurrent stroke.

Section 8.5 Planned interim analyses

The IDMC will monitor the study for greater than expected efficacy and for safety. There will be ~~1~~ 2 formal interim ~~analysis~~ analyses to assess efficacy, which will occur when approximately ~~50% and~~ 50% and 67% of the planned primary efficacy events have accrued. ~~The study may be stopped early, IDMC may recommend early study termination at these interim analyses~~ if there is overwhelming superiority of rivaroxaban ($p < 0.0001$ ~~$Z > 4$~~) for efficacy (e.g., following the conservative ~~Haybittle~~ Peto approach). 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 over ASA.

The IDMC has the flexibility to initiate further interim analyses after the first formal efficacy analysis at 50 %, if deemed appropriate. Given the conservative nature of the monitoring guidelines used in the trial, no adjustment of the significance level for the final analysis is required.

The execution of the interim analyses and decision rules will be specified in the IDMC charter ~~and the SAP for the interim analysis~~.

Section 8.6 Determination of sample size, 3rd paragraph

The number of patients enrolled in the total study may be adjusted or enrollment in the age group 50-59 years may be stopped based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study

Section 9.1 Data recording, 2nd paragraph

Data of 'only screened patients' will be recorded ~~at least~~ as source data, as far as the reason for ~~the premature discontinuation (reason for not randomizing the patient into the study)~~ is identifiable. At minimum, data to be recorded in the eCRF are demographic information (patient number, date of birth/age, sex, race and ethnicity), the reason for ~~premature~~

~~discontinuation-screening failure~~ and date of last visit. These data will be transferred to the respective database.

Section 14.1.1 MRI substudy, 2nd, 3rd, and 7th paragraphs

The primary objective of this substudy is to determine the effect of rivaroxaban compared with aspirin on MRI-defined covert and clinical infarcts (i.e. all incident infarcts) in individuals with a recent ESUS. ...

Secondary objectives will be to determine the effect of rivaroxaban compared to aspirin for reducing covert ~~and clinical~~ infarcts (~~i.e. all incident infarcts~~), the progression of volume of white matter hyperintensities (WMH), functional decline (SAGE), and cognitive decline (DSS, MoCA) in the patients with recent ESUS enrolled in this substudy.

...

Two MRIs will be required:

- Baseline: within 7 days of randomization if the patient is randomized within 30 days of the index event or from 7 days before to 30 days after randomization, if the patient is randomized >30 days after the index event. The MRI for the index event may qualify as the baseline MRI, if the imaging was performed within 7 days ~~of~~ before randomization. In the event of a technically unsatisfactory scan as determined by the core laboratory, the site will have 30 days from notification by the coordinating center to repeat the scan.
- Follow-up: within 30 days of EOT visit in individuals who have not experienced a symptomatic stroke prior to EOT or within 30 days of a symptomatic stroke.

14. Appendices

14.1 Substudies

Two substudies are planned at selected sites. Participation in the substudies is not a requirement. The substudies do not necessarily need to be conducted at the same sites and in the same patients.

Conduct of these substudies is contingent on review and approval by the appropriate Health Authorities and the site's IRB or EC. Patients must sign separate ICFs for participation in these substudies.

14.1.1 MRI substudy - amended

Covert ischemic strokes are defined as strokes not identified clinically at the time of their occurrence but resulting in radiologic evidence of brain infarction. Covert strokes are frequent with a prevalence of 20% at the age of 65 years and are 5 times as common as symptomatic strokes.(30,31) Covert strokes may be manifested as subtle cognitive decline, loss of independence, gait impairment, and falls. The post stroke population is characterized as having a high incidence of these covert infarctions (4% to 24% from 3 cohort studies) and subsequent cognitive and functional impairment.(32-34)

The primary objective of this substudy is to determine the effect of rivaroxaban compared with aspirin on MRI-defined covert and clinical infarcts (i.e. all incident infarcts) in individuals with a recent ESUS.⁵⁰ The primary analysis will be performed on an ITT population (i.e. all patients with baseline and follow-up MRIs, including those with early study drug discontinuation), based on the assessment by an MRI Core facility. An additional analysis will be performed on patients with baseline and follow-up MRIs who take study drug until the efficacy cutoff date.

Secondary objectives will be to determine the effect of rivaroxaban compared to aspirin for reducing covert infarcts, the progression of volume of white matter hyperintensities (WMH), functional decline (SAGE), and cognitive decline (MoCA) in the patients with recent ESUS enrolled in this substudy.⁵¹

Exploratory objectives will be to determine the imaging profile which predicts clinical recurrence as well as the radiologic pattern of recurrent lesions, and to evaluate the predictors of covert infarcts at baseline in the ESUS population.

Approximately 1000 patients will be enrolled in this substudy that is designed to detect a 35% reduction in covert strokes by rivaroxaban with 80% power and a two-sided alpha of 0.05, assuming an annual covert stroke rate of 10% in patients receiving aspirin, a mean follow-up of 24 months, and a drop-out rate of 15%.

The substudy will be conducted at sites with access to 1.5 or 3Tesla MRI. Patients with no contraindication to MRI as assessed using local institutional protocols, e.g., claustrophobia, metal-containing devices or foreign bodies, will be enrolled.

Two MRIs will be required⁵²:

- Baseline: within 7 days of randomization if the patient is randomized within 30 days of the index event or from 7 days before to 30 days after randomization, if the patient is randomized >30 days after the index event. The MRI for the index event may qualify as the baseline MRI, if the imaging was performed within 7 days before randomization. In the event of a technically unsatisfactory scan as determined by the core laboratory, the site will have 30 days from notification by the coordinating center to repeat the scan.
- Follow-up: within 30 days of EOT visit in individuals who have not experienced a symptomatic stroke prior to EOT or within 30 days of a symptomatic stroke.

If a recurrent stroke occurs, all information on MRI or CT performed as routine diagnostic will be collected.

Detailed information regarding image acquisition and processing will be found in an MRI Imaging Manual.

⁵⁰ The primary endpoint was revised with global Protocol Amendment 5 to allow a more sensitive analysis for the entire study population. See Section 13.1.2 for details.

⁵¹ The secondary endpoint was revised with global Protocol Amendment 5 accorded to the revised primary endpoint. The reference to DSS was also removed.

⁵² Additional guidance and clarifications were made to this paragraph with global Protocol Amendment 5. See Section 13.1 for details.

A pooling of data from this MRI substudy with substudy data from the ongoing COMPASS study is planned. The later COMPASS MIND MRI substudy will be conducted in 1500 patients with coronary and peripheral artery disease, who receive either aspirin 100 mg o.d., 5 mg rivaroxaban b.i.d., or 2.5 mg rivaroxaban b.i.d. plus aspirin 100 gm o.d.. The 2 substudies will share the set-up, outcome definitions (MRI and cognitive), and MRI Core Facility.

14.1.2 Biomarker substudy

Biomarker samples (plasma, RNA, and DNA) will be collected in this exploratory substudy to promote, facilitate, and improve individualized healthcare by better understanding/predicting ESUS, recurrent stroke, and associated diseases as well as treatment response. Specifically, the intention is to establish ESUS as a distinct clinical entity in which propensity to coagulation is critical, both as a marker of ESUS and as a risk factor for recurrent stroke.

A total of 18 mL of blood in up to 3000 patients will be collected at the time of randomization for analysis, including, but not limited to: blood biomarker and blood gene expression, as well as genetic determinants.

Biomarkers established in other CV diseases may also play a role in ESUS and recurrent stroke. For example, available data on the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) indicate a link to covert atrial fibrillation. Therefore, potential blood biomarkers that may be measured are: NT-proBNP, hsTroponin, and D-dimer. In addition, other biomarkers of coagulation, pro-thrombotic markers, inflammation markers, and markers linked to stroke or other CV diseases may be analyzed.

Blood gene expression profiles and genetic determinants will be analyzed in a hypothesis free approach with the goal to identify new genes or genetic determinants that are linked to ESUS, recurrent stroke, and other CV diseases.

All genetic information will be doubly de-identified and kept on secure, password protected, computer servers.

Detailed information regarding sampling, processing and storage of blood samples will be found in a Biomarker Manual.



Summary of Revisions

Extracted from page 58 - 70 of Version 2.0 of NAVIGATE ESUS Clinical Study Protocol (2015-11-05)

13. Protocol amendments

13.1 Amendment 5

13.1.1 Overview of changes to the study

The following modifications are introduced in Protocol Version 2.0:

1. The following eligibility criteria were revised (the synopsis, Figure 4-1, Sections 4.1, 5.1.1, 5.1.2, and 6.3 were updated):
 - More details have been provided in the definition of a lacunar stroke in order to avoid protocol deviations.
 - Due to the approximation of the reporting of cervical carotid atherosclerotic stenosis, subjects will be included if there is no stenosis > 50% rather than $\geq 50\%$ to prevent eligible patients from being excluded. Likewise, they will be excluded if there is an intracranial stenosis > 50%.
 - For patients with intracranial arterial occlusions in the territory of the qualifying stroke, it was clarified that a patient is eligible if the investigator believes the occlusion is due to embolism, and not atherosclerotic based on absence of intracranial atherosclerosis elsewhere.
 - For the 24-hour cardiac rhythm monitoring assessment to exclude the presence of AF, an allowance was added to accept a 20-hour recording to reflect routine practice.
 - For the determination of intra-cardiac thrombus, the allowance of transesophageal echocardiography was added as well as transthoracic echocardiography.

The recruitment of patients was changed from *18 years of age or older* to *50 years of age or older* because this will only allow inclusion of patients with a high risk for a recurrent stroke.

Additional clarifications were made to the to the inclusion criterion regarding the patients enrolled with certain risk factors:

- Clarification that covert/silent strokes on neuroimaging and current tobacco smoker count as risk factors.
- Clarification that each risk factor counts separately (ie, “*stroke or TIA prior to index stroke, diabetes, hypertension, and heart failure*” changed to “*stroke or TIA prior to index stroke [includes covert/silent strokes on neuroimaging], diabetes, hypertension, current tobacco smoker, or heart failure*”)
- The rate of recurrent stroke is not known for ESUS patients between ages 50 and 59 who also have additional risk factors and cannot be reliably estimated from available data. Therefore, the age restriction has changed from < 60 years of age with a cap at 10% of the total study population to ≥ 50 years and requirement for an additional risk factor for patients between 50-59 years. Also, clinicians want

to know whether to anticoagulate the substantial fraction of ESUS patients who are under 60 years of age. NAVIGATE ESUS as originally designed (ie, the 10% recruitment cap) would not provide sufficient data to address this question meaningfully.

Clarification was made to the bleeding exclusion criterion 9.

2. The number of patients enrolled in the total study may be adjusted or enrollment in the age group 50-59 years may be stopped based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study. The synopsis (Number of subjects) and Section 8.6 were revised.
3. To allow flexibility, changed that all diagnostic assessments for ESUS *must* be completed before the screening visit to *should* be completed before the screening visit. If prolonged cardiac rhythm monitoring and/or echocardiography are not performed by the time of screening, these assessments can be done during the screening period. The screening period was extended from 4 weeks to 6 weeks (maximum) to allow for this. The Table of procedures and Section 7.1.2.1 were revised.
4. The DSS testing requirement was removed. Due to a missing license, the implementation of this test is not feasible. The Table of procedures and Sections 7.1.2.2, 7.1.2.3, 7.1.2.4, 7.6.1.3, and 14.1.1 were updated.
5. Clarifications were made to avoid misunderstanding regarding the required assessments at EOT. The Table of procedures and 7.1.2.4 were revised.
6. In order to allow more flexibility for patients who are at a rehabilitation clinic after a stroke at the time of Visit 3, a phone call may replace the onsite visit. The Table of procedures and Section 7.1.2.3 (it was also clarified that if a study outcome event is reported ConMeds should be reported) were revised.
7. Corrections were made to data from the PICSS study in Section 1.3.
8. The number of participating countries was updated in Section 5.
9. In Section 5.2, it was clarified that in case a patient is diagnosed with atrial fibrillation with an episode of ≥ 6 minutes during the study, trial medication must be stopped and that a temporary study medication is a “interruption” and not a “discontinuation.” Also, a sentence that stated that patients who permanently discontinue the study will not be reactivated was deleted because this point is covered by exclusion criterion 16 and the statement does not belong in this section.
10. Unblinding will be by a country toll-free help line only (no web-based unblindings). The possibility for treating physicians to unblind was added. Section 6.5.1 was updated.
11. Information about collecting drug interruption details relating to study outcome events was added to Section 6.7.
12. Additional information was provided in Section 6.9 regarding prohibited concomitant medications.

13. Clarification was added for diagnosing AF during the study. In addition to cardiac monitoring, a 12-lead ECG is permissible in lieu of a Holter or other prolonged monitoring method. Section 6.9.2 was revised.
14. The definition of major bleeding was revised for consistency with the ISTH definition. Section 7.5.1 was revised.
15. Additional guidance has been provided in Section 7.5.3.2 for the documentation of intracranial hemorrhage.
16. Dose increases and reductions are not applicable in this study, therefore these options were deleted from the list of choices for “study treatment action” due to AEs in Section 7.5.3.4.
17. The Modified Rankin Score assessment is required 3 months after a recurrent stroke. A range was added (3 to 6 months) to allow flexibility and avoid an additional site visit. The Table of procedures and Sections 7.1.2.3 and 7.6.1.4 were revised.
18. A second interim analysis has been added and the criteria and approach for assessing overwhelming superiority of rivaroxaban has changed as requested by the IDMC. An option to initiate further interim analyses after the first formal efficacy analysis at 50% was added. Details of the interim analyses will no longer be specified in the SAP, but in the IDMC charter only. The synopsis and Section 8.5 was revised.
19. Wording was clarified in Section 9.1 in order to avoid misunderstanding between “premature discontinuation” and “screening failure” and that source data should be documented.
20. The following revisions were made to the MRI substudy in Section 14.1.1:
 - The primary endpoint was changed to allow a more sensitive analysis for the entire study population. The secondary endpoint was updated accordingly.
 - For the baseline MRI, text pertaining to the timing was clarified. A provision was added for a repeat scan in the event the initial scan was not technically acceptable.
 - Further specification was made as to the timing of the follow-up MRI
21. Some typographical errors were corrected and minor editorial and formatting changes were made in Sections 5.1.1, 6.9.2, 7.5.1, 8.4.1, 12, and 14.

13.1.2 Changes to the protocol text

All sections of the protocol affected by the amendment are shown below. Deleted text is ~~crossed out~~ and added text is underlined. Corrections of typographical errors or editorial corrections are not highlighted.

Synopsis, Diagnosis and main criteria for inclusion

- Absence of cervical carotid atherosclerotic stenosis greater than ~~or equal to~~⁴⁶ 50% or occlusion, and

⁴⁶ Symbols are used in the text (ie, \geq and $>$)

- No atrial fibrillation after ≥ 24 -hour cardiac rhythm monitoring (at least 20 hours acceptable), and
- No intra-cardiac thrombus on either transesophageal or transthoracic echocardiography, and

Synopsis, Methodology

Patients who fulfill all inclusion and none of the exclusion criteria after giving informed consent will be randomly allocated 1:1 to either rivaroxaban 15 mg or aspirin 100 mg orally once daily. Randomization will be stratified by country and age <60 and ≥ 60 years. ~~No more than 10% of the total patient population will be randomized into the age group <60 years.~~

Synopsis, Number of subjects

The number of patients enrolled in the total study may be adjusted or enrollment in the age group 50-59 years may be stopped based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study.

Synopsis, Plan for statistical analysis

There will be ± 2 formal interim ~~analysis~~ analyses to assess efficacy and stop for overwhelming superiority, which will occur when approximately 50% and 67% of the planned primary efficacy outcomes have accrued.

Table of procedures

	Screen	Random	Treatment Phase						Washout
	V1	V2	V3	V4	V5	V6	V7-V [∞]	EOT ^a	Safety Visit
Timelines	-4-6 to 0 wks^b	0	1 Mo	3 Mo	6 Mo	12 Mo	every 6 Mo	End of Treat	1 Mo post EOT
Visit Window (weeks)			±1	±4	±4	±4	±4		±1
Type of Visit	Visit	Visit	Visit_L	☎	Visit	Visit	Visit	Visit	☎
.....									
EQ-5D MoCA, DSS, and SAGE		• •			•	•	•	•	

Abbreviations: EOT = end of treatment; Mo = month; V = visit, ☎ = telephone contact; eGFR = estimated glomerular filtration rate; ConMeds = Concomitant medications; MoCA = Montreal Cognitive Assessment; DSS = Digit Symbol Substitution test; SAGE = Standard Assessment of Global-Activities in the Elderly; EQ-5D = European Quality of Life-5 Dimensions questionnaire; SAE = serious adverse event; TIA = transient ischemic attack; MI = myocardial infarction

- a End of treatment visit is to be performed within the trial close-out window before the end of the study (efficacy cut-off date) or once the patient has permanently discontinued study medication and when no further visits at the site will be performed
- b Screening visit can be the same as randomization visit, if all required tests for eligibility criteria are available at screening visit. Maximum screening period -4-6 weeks.

.....

- k For definition see Section 7.6.1.4. In case of recurrent stroke to be done at 7 days post stroke or at discharge from hospital in case this occurs before 7 days and again at 3-6 months post stroke

L Patients who are at a rehabilitation or other clinic at the time of the 1 month visit (Visit 3), more flexibility will be allowed and this visit can be performed as a phone call instead of an onsite visit.

.....

Section 1.3 Studies assessing the efficacy of anticoagulation for secondary prevention of embolic stroke of undetermined source, last sentence of 3rd paragraph

In addition, in the PICSS study, ~~260~~ 98 participants with a patent foramen ovale, the primary outcome (2 year rate of recurrent ischemic stroke or death) was halved in those assigned to warfarin (9.5% warfarin vs. 17.9% ASA).

Section 4.1 Overview, 4th and 5th paragraphs

Patients will be ~~enrolled~~ randomized as early as possible after the required diagnostic evaluation is complete and eligibility criteria are fulfilled. The goal is that the majority of patients are enrolled within 3 months, and fewer patients between 3 and 6 months.

Randomization will be stratified by country and age <60 and ≥60 years. ~~No more than 10% of the total patient population will be randomized into the age group <60 years, as patients with <60 years have a lower risk for recurrent stroke.~~ Patients < 60 years will need to have at least one risk factor such as stroke (includes covert/silent strokes on neuroimaging) or TIA prior to index stroke, diabetes, hypertension, current tobacco smoker or and heart failure.

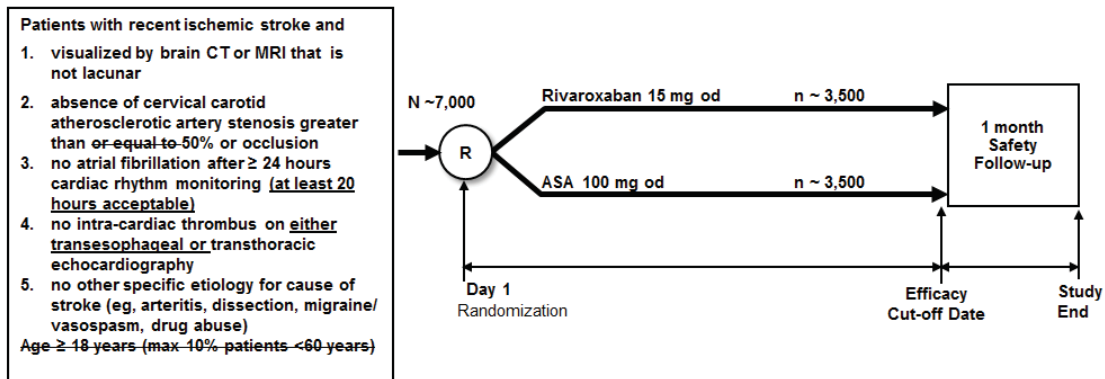


Figure 4-1

Section 5 Study population

This Phase III, multi-national, study will be conducted in ~~25 to 30~~ approximately 30 countries worldwide in approximately 7000 patients recruited primarily from hospital-based stroke units.

Section 5.1.1 Inclusion criteria

1. Embolic stroke of undetermined source (ESUS) defined as:
 - Recent ischemic stroke (including TIA with positive neuroimaging) visualized by brain CT or MRI that is not lacunar (i.e., lacunar infarcts are subcortical infarcts ≤ 1.5 cm in the territory of middle cerebral artery or pons; infarcts involving the cerebellum or lateral medulla are not considered as lacunar infarcts). Patients with multiple simultaneous acute lacunar infarcts on DWI imaging may be included. In case of embolic large artery occlusions clearly documented on angiography who undergo successful recanalization, visualization of infarct on neuroimaging is not mandated, and
 - Absence of cervical carotid atherosclerotic stenosis (or vertebral and basilar artery atherosclerotic stenosis in case of posterior circulation stroke), that is greater than ~~or equal to~~ ⁴⁷ 50%, or occlusion in arteries supplying the area of ischemia in CT or magnetic resonance (MR) angiography or conventional angiography or ultrasound, and
 - No history of AF, no documented AF on 12-lead electrocardiogram (ECG) or episode of AF lasting 6 minutes or longer detected after ≥ 24 -hour cardiac rhythm monitoring (Holter or telemetry; at least 20 hours acceptable), and
 - No intra-cardiac thrombus on either transesophageal or transthoracic echocardiography, and
 - ...

⁴⁷ Symbols are used in the text (ie, \geq and $>$)

4. Age ~~≥18~~ 50 years (~~or respective country specific legal lower age limit if this is >18 years~~)
5. For patients with age ~~<60~~ 50-59 years at least one of the following risk factors: stroke or TIA prior to index stroke (includes covert/silent strokes on neuroimaging), diabetes, hypertension, current tobacco smoker ~~and~~ or heart failure.

Section 5.1.2 Exclusion criteria

2. If imaging of intracranial arteries is performed by CT or MR angiography or transcranial Doppler: greater than ~~or equal to~~⁴⁸ 50% luminal stenosis or occlusion in arteries supplying the area of ischemia
9. Active bleeding, major bleeding within last 6 months, ~~history of primary intracranial hemorrhage~~ or high risk for serious bleeding contraindicating anticoagulant or antiplatelet therapy or history of primary intracranial hemorrhage

Section 5.2 Discontinuation of patients from study treatment, 2nd, 3rd, and 8th paragraphs

Patients may discontinue study medication at their own request and without giving reasons (even though providing a reason is encouraged), based on the investigator's judgment, if the patient is pregnant, or at the request of the sponsor (exceptional circumstances). In case a patient is diagnosed with atrial fibrillation with an episode of at least 6 minutes during the study trial medication must be stopped (see section 6.9.2)....

In case of a temporary study medication ~~discontinuation~~ interruption for any reason, study medication will be restarted as soon as medically justified in the opinion of the investigator. There is no defined maximum limit for temporary treatment interruption.

....

~~Patients who permanently discontinue the study for any reason will not be reactivated.~~

Section 6.3 Treatment assignment, sentence deleted

~~No more than 10% of the total patient number will be randomized into the age group < 60 years.~~

Section 6.5.1 Emergency unblinding by the investigator

Unnecessary unblinding should be avoided and should only be undertaken by the investigator or the treating physician when it is essential for the patient's safety. In such a situation, the investigator will be able to unblind the patient via the ~~IXRS system~~ country toll-free help line.

Section 6.7 Treatment compliance

First dose, last dose, and any dose interruptions of study medication due to AEs, study outcome events, or of >7 days for any other reason will be reported in the eCRF.

Section 6.9 Prior and concomitant therapy

⁴⁸ Symbols are used in the text (ie, ≥ and >)

No specific concomitant medications are prohibited other than strong inhibitors of both CYP3A4 and Pgp inhibitors. This includes human immunodeficiency virus protease inhibitors and the following azole antimycotics agents: ketoconazole, itraconazole, voriconazole, or posaconazole, if used systemically. However, fluconazole is allowed.

In addition, concomitant use with antiplatelets and anticoagulants is outlined in the sections below.

Section 6.9.2 Guidance for management of participants who have atrial fibrillation identified during the study

If a patient is diagnosed with AF during the study that requires oral anticoagulation according to the investigator's judgment, the patient will stop double blind study medication. Per protocol, study medication must be permanently discontinued if AF is seen in a 12-lead ECG or if an AF episode of greater than or equal⁴⁹ to 6 minutes is identified during cardiac monitoring.

Section 7.1.2.1 Visit 1 (screening)

Visit 1 will be used to assess the eligibility of the patient. After obtaining signed informed consent, the investigator will review the diagnostic tests required to diagnose ESUS. All diagnostic assessments for ESUS ~~must~~ should be completed before the screening visit. If prolonged cardiac rhythm monitoring and/or echocardiography are not performed at time of screening, this can be done during the screening period.

The screening period will be 6 weeks maximum.

Section 7.1.2.2 Visit 2 (randomization visit)

Outcomes research questionnaires (Section 7.6.1) will be completed by the patient:

- European Quality of Life-5 Dimensions (EQ-5D) Questionnaire
- Montreal Cognitive Assessment (MoCA)
- ~~Digit Symbol Substitution (DSS) test~~
- Standard Assessment of Global-Activities in the Elderly (SAGE) questionnaire

Section 7.1.2.3 Regular study visits (visits 3 and onward), 1st, 4th, 5th and 6th paragraphs

Patients will return to the study clinic at 1 month, 6 months, and then every 6 months. Patients who are at a rehabilitation or other clinic at the time of the 1 month visit (Visit 3), more flexibility will be allowed and this visit can be performed as a phone call instead of an onsite visit. At 3 months, the patient will receive a telephone call to obtain safety and outcome data and reinforce adherence to study medication and to avoiding non-study ASA.

...

Concomitant medications and weight will be collected once per year. If an SAE or study outcome event is reported, the use of any additional ConMeds should be recorded at that time

⁴⁹ Symbols are used in the text (ie, > and ≥).

The outcomes research questionnaires (MoCA, ~~DSS~~, and SAGE) will be completed by the patient at the 1 year visit only. The EQ-5D will be completed every 6 months.

If a recurrent stroke is reported, the modified Rankin Score is to be assessed at 7 days post stroke or at hospital discharge, if this occurs before 7 days, and again at 3-6 months post stroke. The modified Rankin score is also to be recorded at 1 year after stroke.

Section 7.1.2.4 End of treatment (EOT) visit

~~When the sponsor announces~~ Within the trial close-out window prior to the end of the study (efficacy cut-off date), all patients must return to the clinic within 6 weeks in order to make a final assessment. In addition, for patients that permanently discontinued study medication and when further follow-up will no longer be done by site visits and rather by phone or third party contact, the patient will be encouraged to come for the EOT visit as soon as possible after discontinuation of study medication. For these patients a final vital status and outcome events will be collected during the trial close-out window. At this EOT visit, study procedures will include the collection of efficacy and safety outcome data, (S)AEs, vital signs, ConMeds, EQ-5D, MoCA, ~~DSS~~ and SAGE questionnaires, and modified Rankin score. In addition, the study staff will collect the patient's empty and unused study medication bottles to allow final drug accountability and compliance checks.

Section 7.5.1 Primary safety variable

- Symptomatic bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), and/or

Section 7.5.3.2 Adverse event reporting, 3rd bullet

- All bleeding events including fatal bleeding will be captured in the eCRF (Bleeding page). Serious adverse events which are bleeding terms will not be reported to the sponsor's PV Department in an expedited manner. Symptomatic intracerebral/intraparenchymal hemorrhages as well as symptomatic subarachnoid hemorrhages will be captured as bleeding and as stroke. All subdural/epidural hematoma and asymptomatic intracranial bleeding are only reported as bleeding.

Section 7.5.3.4 Intensity of an adverse event, action taken, and outcome

Any action on study treatment to resolve the AE is to be documented as: study drug withdrawn, interrupted, ~~dose reduced~~, dose not changed, ~~dose increased~~, not applicable, or unknown.

Section 7.6.1.3 Montreal Cognitive Assessment, ~~Digit Symbol Substitution test~~, and Standard Assessment of Global-Activities in the Elderly

The MoCA ~~and DSS~~ will be included in the study to assess cognition and the SAGE questionnaire will be used to assess functional outcome. These tests and questionnaires will be administered at Day 0 (randomization), 1 year, and at the EOT visits. The patients will be asked to independently complete the MoCA ~~and DSS~~ tests to the best of their ability. Otherwise, the reason for not completing must be documented. The SAGE questionnaire may be completed with the help of the study staff.

Section 7.6.1.4 Modified Rankin Score

In addition to the regular assessments at screening, 1 year, and EOT, the Modified Rankin Score will be assessed by the investigator at 7 days or at discharge, if this occurs before 7 days, and again at 3-6 months after a recurrent stroke.

Section 8.5 Planned interim analyses

The IDMC will monitor the study for greater than expected efficacy and for safety. There will be ~~1~~ 2 formal interim ~~analysis~~ analyses to assess efficacy, which will occur when approximately ~~50% and~~ 50% and 67% of the planned primary efficacy events have accrued. ~~The study may be stopped early, IDMC may recommend early study termination at these interim analyses~~ if there is overwhelming superiority of rivaroxaban ($p < 0.0001$ ~~$Z > 4$~~) for efficacy (e.g., following the conservative ~~Haybittle~~ Peto approach). 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 over ASA.

The IDMC has the flexibility to initiate further interim analyses after the first formal efficacy analysis at 50 %, if deemed appropriate. Given the conservative nature of the monitoring guidelines used in the trial, no adjustment of the significance level for the final analysis is required.

The execution of the interim analyses and decision rules will be specified in the IDMC charter ~~and the SAP for the interim analysis~~.

Section 8.6 Determination of sample size, 3rd paragraph

The number of patients enrolled in the total study may be adjusted or enrollment in the age group 50-59 years may be stopped based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study

Section 9.1 Data recording, 2nd paragraph

Data of 'only screened patients' will be recorded ~~at least~~ as source data, as far as the reason for ~~the premature discontinuation (reason for not randomizing the patient into the study)~~ is identifiable. At minimum, data to be recorded in the eCRF are demographic information (patient number, date of birth/age, sex, race and ethnicity), the reason for ~~premature~~

~~discontinuation-screening failure~~ and date of last visit. These data will be transferred to the respective database.

Section 14.1.1 MRI substudy, 2nd, 3rd, and 7th paragraphs

The primary objective of this substudy is to determine the effect of rivaroxaban compared with aspirin on MRI-defined covert and clinical infarcts (i.e. all incident infarcts) in individuals with a recent ESUS. ...

Secondary objectives will be to determine the effect of rivaroxaban compared to aspirin for reducing covert ~~and clinical~~ infarcts (~~i.e. all incident infarcts~~), the progression of volume of white matter hyperintensities (WMH), functional decline (SAGE), and cognitive decline (DSS, MoCA) in the patients with recent ESUS enrolled in this substudy.

...

Two MRIs will be required:

- Baseline: within 7 days of randomization if the patient is randomized within 30 days of the index event or from 7 days before to 30 days after randomization, if the patient is randomized >30 days after the index event. The MRI for the index event may qualify as the baseline MRI, if the imaging was performed within 7 days ~~of~~ before randomization. In the event of a technically unsatisfactory scan as determined by the core laboratory, the site will have 30 days from notification by the coordinating center to repeat the scan.
- Follow-up: within 30 days of EOT visit in individuals who have not experienced a symptomatic stroke prior to EOT or within 30 days of a symptomatic stroke.

14. Appendices

14.1 Substudies

Two substudies are planned at selected sites. Participation in the substudies is not a requirement. The substudies do not necessarily need to be conducted at the same sites and in the same patients.

Conduct of these substudies is contingent on review and approval by the appropriate Health Authorities and the site's IRB or EC. Patients must sign separate ICFs for participation in these substudies.

14.1.1 MRI substudy - amended

Covert ischemic strokes are defined as strokes not identified clinically at the time of their occurrence but resulting in radiologic evidence of brain infarction. Covert strokes are frequent with a prevalence of 20% at the age of 65 years and are 5 times as common as symptomatic strokes.(30,31) Covert strokes may be manifested as subtle cognitive decline, loss of independence, gait impairment, and falls. The post stroke population is characterized as having a high incidence of these covert infarctions (4% to 24% from 3 cohort studies) and subsequent cognitive and functional impairment.(32-34)

The primary objective of this substudy is to determine the effect of rivaroxaban compared with aspirin on MRI-defined covert and clinical infarcts (i.e. all incident infarcts) in individuals with a recent ESUS.⁵⁰ The primary analysis will be performed on an ITT population (i.e. all patients with baseline and follow-up MRIs, including those with early study drug discontinuation), based on the assessment by an MRI Core facility. An additional analysis will be performed on patients with baseline and follow-up MRIs who take study drug until the efficacy cutoff date.

Secondary objectives will be to determine the effect of rivaroxaban compared to aspirin for reducing covert infarcts, the progression of volume of white matter hyperintensities (WMH), functional decline (SAGE), and cognitive decline (MoCA) in the patients with recent ESUS enrolled in this substudy.⁵¹

Exploratory objectives will be to determine the imaging profile which predicts clinical recurrence as well as the radiologic pattern of recurrent lesions, and to evaluate the predictors of covert infarcts at baseline in the ESUS population.

Approximately 1000 patients will be enrolled in this substudy that is designed to detect a 35% reduction in covert strokes by rivaroxaban with 80% power and a two-sided alpha of 0.05, assuming an annual covert stroke rate of 10% in patients receiving aspirin, a mean follow-up of 24 months, and a drop-out rate of 15%.

The substudy will be conducted at sites with access to 1.5 or 3Tesla MRI. Patients with no contraindication to MRI as assessed using local institutional protocols, e.g., claustrophobia, metal-containing devices or foreign bodies, will be enrolled.

Two MRIs will be required⁵²:

- Baseline: within 7 days of randomization if the patient is randomized within 30 days of the index event or from 7 days before to 30 days after randomization, if the patient is randomized >30 days after the index event. The MRI for the index event may qualify as the baseline MRI, if the imaging was performed within 7 days before randomization. In the event of a technically unsatisfactory scan as determined by the core laboratory, the site will have 30 days from notification by the coordinating center to repeat the scan.
- Follow-up: within 30 days of EOT visit in individuals who have not experienced a symptomatic stroke prior to EOT or within 30 days of a symptomatic stroke.

If a recurrent stroke occurs, all information on MRI or CT performed as routine diagnostic will be collected.

Detailed information regarding image acquisition and processing will be found in an MRI Imaging Manual.

⁵⁰ The primary endpoint was revised with global Protocol Amendment 5 to allow a more sensitive analysis for the entire study population. See Section 13.1.2 for details.

⁵¹ The secondary endpoint was revised with global Protocol Amendment 5 accorded to the revised primary endpoint. The reference to DSS was also removed.

⁵² Additional guidance and clarifications were made to this paragraph with global Protocol Amendment 5. See Section 13.1 for details.

A pooling of data from this MRI substudy with substudy data from the ongoing COMPASS study is planned. The later COMPASS MIND MRI substudy will be conducted in 1500 patients with coronary and peripheral artery disease, who receive either aspirin 100 mg o.d., 5 mg rivaroxaban b.i.d., or 2.5 mg rivaroxaban b.i.d. plus aspirin 100 gm o.d.. The 2 substudies will share the set-up, outcome definitions (MRI and cognitive), and MRI Core Facility.

14.1.2 Biomarker substudy

Biomarker samples (plasma, RNA, and DNA) will be collected in this exploratory substudy to promote, facilitate, and improve individualized healthcare by better understanding/predicting ESUS, recurrent stroke, and associated diseases as well as treatment response. Specifically, the intention is to establish ESUS as a distinct clinical entity in which propensity to coagulation is critical, both as a marker of ESUS and as a risk factor for recurrent stroke.

A total of 18 mL of blood in up to 3000 patients will be collected at the time of randomization for analysis, including, but not limited to: blood biomarker and blood gene expression, as well as genetic determinants.

Biomarkers established in other CV diseases may also play a role in ESUS and recurrent stroke. For example, available data on the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) indicate a link to covert atrial fibrillation. Therefore, potential blood biomarkers that may be measured are: NT-proBNP, hsTroponin, and D-dimer. In addition, other biomarkers of coagulation, pro-thrombotic markers, inflammation markers, and markers linked to stroke or other CV diseases may be analyzed.

Blood gene expression profiles and genetic determinants will be analyzed in a hypothesis free approach with the goal to identify new genes or genetic determinants that are linked to ESUS, recurrent stroke, and other CV diseases.

All genetic information will be doubly de-identified and kept on secure, password protected, computer servers.

Detailed information regarding sampling, processing and storage of blood samples will be found in a Biomarker Manual.



Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS), comparing rivaroxaban 15 mg once daily with aspirin 100 mg (NAVIGATE ESUS)

Secondary prevention of stroke in patients with a recent ESUS

Bayer study drug BAY 59-7939/rivaroxaban

Clinical study phase: III **Date:** 2 Mar 2015

Study No.: 16573 **Version:** 1.0

Authors: Bodo Kirsch, Balakumar Swaminathan,
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Abbreviations

AE	Adverse event
AF	Atrial fibrillation
APCC	Activated prothrombin complex concentrate
ARISTOTLE	Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE)
ASA	Acetylsalicylic acid; aspirin
AVERROES	A Phase III Study of Apixaban in Patients With Atrial Fibrillation (AVERROES)
BHC	Bayer HealthCare
b.i.d.	Twice daily
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence interval
ConMed	Concomitant medication
CRO	Contract research organization
CSR	Clinical Study Report
CT	Computed tomography
cTn	Cardiac troponin
CV	Cardiovascular
CYP3A4	Cytochrome P450 isoenzyme 3A4
DSS	Digit Symbol Substitution test
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EINSTEIN	Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis -The EINSTEIN DVT Study
e.g.	for example
eGFR	Estimated glomerular filtration rate
ENGAGE	Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (EngageAFTIMI48)
EOT	End-of-treatment
EQ-5D	European Quality of Life-5 Dimensions questionnaire
ESUS	Embolic stroke of undetermined source
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
H	Hypothesis
HDPE	High-density polyethylene
HEOR	Health Economics, Outcomes & Reimbursement
HR	Hazard ratio
ICAC	Independent Central Adjudication Committee
ICF	Informed consent form
ICH	International Conference on Harmonisation
IB	Investigator's brochure
i.e.	id est (that is)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	International ratio

IRB	Institutional Review Board
ISAC	Independent Statistical Analysis Centre
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-to-treat
IxRS	Interactive web/voice response system
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
Mo	Month
MoCA	Montreal Cognitive Assessment
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Score
NSAID	Non-steroid anti-inflammatory drug
NV	Corporation (in The Netherlands)
NVAF	Non-valvular atrial fibrillation
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
o.d.	Once daily
OMP	Ortho McNeil Pharmaceuticals
p	p-value
PCC	Prothrombin complex concentrate
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
P-gp	P-glycoprotein
PICSS	Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS)
PID	Patient identification
PPS	Per protocol set
PT	Prothrombin time
PV	Pharmacovigilance
QA	Quality assurance
RRR	Relative risk reduction
S	Survival
SAE	Serious adverse event
SAF	Safety set
SAGE	Standard Assessment of Global-Activities in the Elderly
SAP	Statistical analysis plan
SC	Steering Committee
SUSAR	Suspected unexpected serious adverse reaction
TIA	Transient ischemic attack
USA	United States of America
V	Visit
VKA	Vitamin K antagonist
vs.	versus
VTE	Venous thromboembolism
WARSS	Warfarin-Aspirin Recurrent Stroke Study
WHO	World Health Organization
WMH	White matter hyperintensities

1. Introduction

Globally, cerebrovascular disease (stroke) is the second leading cause of death and the fourth leading cause of disease burden as measured in disability-adjusted life years. The World Health Organization (WHO) estimates that worldwide 16 million people suffer a first ever stroke annually, with 5 million deaths due to stroke in 2005, and another 5 million left permanently disabled.

Recently, the concept of “embolic stroke of undetermined source” (ESUS) has developed, recognizing that except for lacunar strokes, most cryptogenic strokes are embolic. The sources of embolism underlying ESUS include the heart (either within the heart or via paradoxical embolism from a venous source), aortic arch, or the large cervical and cerebral arteries.

Randomized clinical trials have addressed secondary prevention for all major ischemic stroke subtypes except for cryptogenic stroke or ESUS. Among the estimated 300,000 patients with acute cryptogenic stroke annually in North America and Europe there has been little progress in secondary prevention during the past two decades. There is a substantial unmet medical need in this patient population, as despite treatment with antiplatelets, the recurrent stroke rate still remains at 3 to 6% annually.

There is persuasive evidence that the dominant underlying pathophysiology of ESUS is embolism (cardioembolic, arteriogenic, or paradoxical). Improvements in imaging technology and an increased appreciation of the underlying pathophysiology of ESUS have resulted in better understanding and in a practical clinical definition of ESUS so that these patients can be reliably identified.

Based on evidence for superior efficacy of warfarin anticoagulation over ASA for other types of embolic stroke, anticoagulation is expected to be superior to ASA in ESUS patients. The direct oral Factor Xa-inhibitor rivaroxaban, when compared with VKAs, has been demonstrated to be effective against embolic stroke related to non-valvular AF. Because of its predictable anticoagulant activity and low risk of intracranial hemorrhage, it is expected that rivaroxaban will reduce stroke recurrence in ESUS compared with ASA, and with an acceptable safety (bleeding) profile. Rivaroxaban has also been shown to be efficacious for the treatment of DVT and PE, prevention of recurrent DVT and PE, prevention of VTE following total hip and total knee replacement, and also for prevention of atherothrombotic events after an acute coronary syndrome with elevated cardiac biomarker. Rivaroxaban has no dietary restrictions and only few drug interactions and does not require routine coagulation laboratory monitoring.

Given these considerations, a large, multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study comparing rivaroxaban 15 mg o.d. with

ASA 100 mg o.d. for the secondary prevention of stroke and prevention of systemic embolism will be conducted.

This core SAP is based on the Clinical Study Protocol BAY 59-7939/16573 version 1.0 from 16 July 2014 and contains definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety for the ESUS study. It provides a technical and detailed elaboration of the principal features of the planned analyses, e.g., censoring schemes for time-to-event variables. Amendments and/or appendices to this core SAP may be used to provide more details on the coding guidelines, data-handling, and output tables and figures.

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

2. Study Objectives

The primary efficacy objective is:

- To evaluate whether rivaroxaban is superior to aspirin in reducing the risk of recurrent stroke and systemic embolism in patients with a recent ESUS

The secondary efficacy objective is:

- To evaluate whether rivaroxaban is superior to aspirin in reducing the risk of cerebrovascular events, cardiovascular events, and mortality in patients with a recent ESUS

The safety objective is to document the incidence of clinically relevant bleeding.

3. Study Design

This is a multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study in patients with a recent ESUS.

Following provision of informed consent, patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomly allocated by an interactive voice/web response system (IxRS) to either rivaroxaban 15 mg o.d. or ASA 100 mg o.d. in a 1:1 ratio. No dose adjustment will be made for patients with mild or moderate renal impairment.

Patients may be randomized and receive the first study medication intake between 7 days and 6 months after the index stroke event. In case of minor strokes (National Institutes of Health Stroke Score [NIHSS] ≤ 3), study medication may be initiated as early as 3 days after stroke onset if all eligibility assessments have been completed. In the presence of hemorrhagic transformation on the qualifying brain imaging study or if intravenous thrombolysis therapy was given for the index stroke, study medication will not be initiated before 10 days after the acute stroke event unless a repeat CT or magnetic resonance imaging (MRI) performed before randomization documents the absence of new or extension of hemorrhage.

Patients will be enrolled as early as possible after the required diagnostic evaluation is complete and eligibility criteria are fulfilled. The goal is that the majority of patients are enrolled within 3 months, and fewer patients between 3 and 6 months.

Randomization will be stratified by country and age <60 and ≥60 years. No more than 10% of the total patient population will be randomized into the age group <60 years, as patients with <60 years have a lower risk for recurrent stroke. Patients < 60 years will need to have at least one risk factor such as stroke or TIA prior to index stroke, diabetes, hypertension, and heart failure.

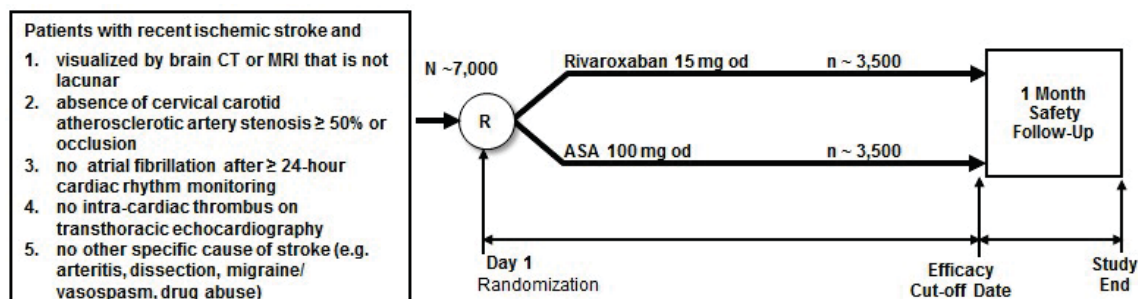
At randomization, patients will receive study medication and instructions for its administration. Thereafter, patients will return to the clinic at 1, 6, and 12 months and then every 6 months until the end of study (efficacy cut-off date) is announced. At 3 months, the patient will be contacted by telephone. Throughout the study and at clinic visits, patients will be assessed for efficacy (stroke, systemic embolism, MI, CV death, or all-cause mortality) and safety (vital signs, bleeding, serious adverse events [SAEs] which are not outcome events, non-serious adverse events [AE]s leading to permanent discontinuation of study treatment, and any non-serious AEs of particular concern to the investigator).

The trial will continue until approximately 450 patients are anticipated to have experienced a positively adjudicated primary efficacy outcome event. This is anticipated to occur approximately 3 years after the first patient is randomized, but may vary depending on the recruitment rate as well as the primary event rate. A telephone safety visit will be performed 1 month after the end-of-treatment (EOT) visit.

Patients permanently discontinuing study treatment will continue to be followed, and outcome events and vital status must be assessed in these patients until the end of the study via either clinic visits or telephone contacts.

All efficacy and safety analyses are based on time from randomization to time of first event. Suspected clinical study outcomes will be assessed by the ICAC, which will be blinded to treatment allocation. Adjudicated results will be the basis for the final analyses. The IDMC will monitor patient safety during the study and give recommendations to the SC and sponsor.

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



The target patient population comprises patients with a recent ESUS. These patients have substantial risk for recurrent stroke and other thromboembolic events despite antiplatelet therapy, the current standard of care. A double-blind, randomized trial design comparing rivaroxaban with ASA is deemed the most appropriate design to allow for an unbiased evaluation of rivaroxaban as a treatment option for this patient population in an international trial.

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 final efficacy outcome event has been adjudicated for patients from all participating clinical sites (EU and non-EU).

4. General Statistical Considerations

4.1 General Principles

All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data, as appropriate. Frequency tables will be generated for categorical data. The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

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

An excessive rate of patient discontinuations from either treatment or study follow up may render the trial non-interpretable. In this study, outcome events and vital status data will be collected until the end of the study, even if patients are no longer taking study medication. This means that clinical data from all randomized patients will be collected at trial close-out as far as possible.

A subject who signed an informed consent form, and, for any reason (e.g., failure to satisfy the in- and exclusion criteria) terminates the study without being randomized is regarded as a “screening failure”.

A randomized subject who permanently discontinues study treatment before their End of treatment Visit for any reason is defined as having had a permanent discontinuation of study medication (including subjects who were randomized but never started taking any study medication). The reason for permanent discontinuation of study medication will be collected.

For subjects who permanently discontinue study medication, different options of follow-up will be discussed to collect outcome events and vital status. This can include regular study visits, regular phone calls with the patient or otherwise with the general practitioner or family

relative, or a contact at the end of the study. Patients who do not agree to attend regular study visits the investigator will encourage to come to at least one final visit to perform assessments to the greatest extent possible as outlined for the End of treatment Visit.

However, all randomized subjects will be encouraged to remain on study treatment and under observation for the full duration of the study. Discontinuation of study treatment is not the equivalent to withdrawal of informed consent. In cases where subjects indicate they do not want to “continue”, investigators must determine whether this refers to discontinuation of study treatment, unwillingness to attend follow-up visits, unwillingness to have telephone contact, unwillingness to have any contact with study personnel, or unwillingness to allow contact with a third party (e.g., family member, doctor). Every effort will be made to continue to follow the subject and survival status information must be determined for all subjects at the end of the study. The expectation is that only very few subjects will have incomplete follow-up (in any form) within this trial.

A subject will be declared to have incomplete follow-up or to be lost to follow-up (i.e., to be completely non-compliant to follow-up) if, despite of all possible efforts, all investigators, dedicated site staff, and/or PHRI Project Office (as applicable and as local regulations allow) are not able to contact the subject or a third party (e.g., family member, doctor). Every possible effort will be made to contact the subject or a third party and to determine the endpoint and survival status and reason for discontinuation as local law permits. If it is documented in the database that the subject is alive at the end of the study, the subject will not be classified as lost to follow-up, but as alive.

4.3 Handling of Missing Data

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

Missing or incomplete event dates

When an event date is not known, the site investigator will be asked to provide a best estimate as to when the event occurred. Even though the exact date of an event is unknown, the investigator often does know some information that would indicate the approximate date, such as the first week of a month, in the fall of a year, or the middle of a particular year, or at least the date when the subject was last seen or contacted. This information can be meaningfully incorporated into the estimated date recorded, as this is likely to be closer to the true date than any produced by an uninformed computer program. This estimated date should be the middle date within the period that the event is known to have occurred. If the event is known to have occurred in the first week of a month, then the date in the middle of that week should be recorded as the estimate. If it occurred in the fall of a year, then the middle date in the fall is the appropriate estimate. If no information is known then the date in the middle of the plausible time period should be given, based on the last contact with the subject prior to the event (start date of plausible time period) and the date of contact when information about

the event was known (end date of plausible time period). This method for date estimation has been used in many studies and is recommended by [Dubois](#).

If the date/time information is not sufficient to determine whether an event occurred prior or after randomization, the event is considered as an outcome, to be conservative. The event start date will be imputed no earlier than randomization date.

4.4 Interim Analyses and Data Monitoring

The IDMC will monitor the study for efficacy and for safety by reviewing unblinded event rates.

There will be 1 formal interim analysis to assess efficacy, which will occur when approximately 67% of the planned primary efficacy events have accrued. The study may be stopped early, if there is overwhelming superiority of rivaroxaban ($p < 0.0001$) for efficacy (e.g., following the conservative Haybittle-Peto approach). 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 over ASA.

Given the conservative monitoring boundary and only one interim analysis, the type I error level adjustment for the final analysis won't be necessary.

The execution of the interim analyses and decision rules will be specified in the IDMC charter and the SAP for the interim analysis.

All (unblinded) statistical analyses for the IDMC and the interim analysis will be performed by the ISAC (Independent Statistical Analysis Centre).

The steering committee will review overall blinded event rates to ensure that they meet protocol projections. If overall event rates are lower than expected, consideration will be given to altering the trial design, such as increasing the sample size or extending the study duration without knowledge of any treatment effect.

4.5 Data Rules

4.5.1 Analysis Dates

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

- Efficacy cut-off date:
The efficacy cut-off date is the predicted date when at least 450 subjects are expected to have experienced an event for the primary efficacy outcome. This date will be chosen by the study committee and all sites will be notified. It is the last calendar date acceptable for counting events within the primary analysis.

- Trial close-out window:
The Trial close-out window is the time period when all subjects are to return to the clinic for an End of treatment Visit. The start date of this window is a fixed time prior to the efficacy cut-off date as defined in the protocol. The end date is the efficacy cut-off date.

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

- Randomization date:
The date of randomization to antithrombotic study treatment of the subject.
- End of treatment (EOT) Visit date:
This is the date of the EOT Visit for the individual subject.
After the announcement of the end of the study, all subjects are to return to the clinic for their EOT Visit within the pre-specified window (Trial close-out window).
If subjects do not have an EOT visit, the date will be missing.
- Date of the last contact prior to efficacy cut-off:
This date is defined as
 - the EOT visit date, if the subject attends his/her EOT visit within the Trial close-out window or
 - the date of the last documented contact with the subject or a third party (including data on subject survival status) prior to the efficacy cut-off date, if the subject does not attend his/her EOT visit within the Trial close-out window.For subjects who die (a) after randomization but before the beginning of the Trial close-out window or (b) during the Trial close-out window but before their planned EOT visit takes place, the date of the last contact prior to efficacy cut-off is set to the death date.
- Date of the last trial contact:
The date of the last documented contact with the subject or a third party (including data on subject survival status).
For subjects who die after randomization the date of the last contact is set to the death date.
- Date of first double-blind dose of antithrombotic study treatment:
The date of the first dose of rivaroxaban / aspirin study medication.
- Date of last double-blind dose of antithrombotic study treatment:
The date of the last dose of rivaroxaban / aspirin study medication.
For a subject with permanent discontinuation of any study medication, the corresponding last dose date(s) will be obtained from the CRF “Study Medication Discontinuation/Restart Report”. If study medication was continued until the EOT visit, the date of the last dose of the corresponding study medication will be as reported on the EOT visit CRF.

If missing or incomplete, the date of last double-blind dose of antithrombotic study treatment is set to the latest logically possible date of antithrombotic study medication administration on or before the earliest of the subject's following dates, the date of last trial contact, the date of death, or the efficacy cut-off date, and no earlier than the randomization date.

4.5.2 Data Scopes

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

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

The ITT data scope includes all outcome events observed from randomization until the End of treatment visit within the Trial close-out window, or for patients without such visit until last trial contact or efficacy cut-off date, whatever comes first. This will be the primary data scope for the analyses.

Analyses according to the intention-to-treat (ITT) principle will be based on the intention-to-treat analysis set (see section 5.1.1) and will include all outcome events that occur after the date and time of randomization and up until the EOT visit (inclusive) for each subject, if the EOT visit date is in the Trial close-out window. Events occurring after this EOT visit will not be counted for primary analysis. For subjects who are unable to attend the EOT Visit in time and had no contact within the Trial close-out window, events up to the efficacy cut-off date will be included in the analysis in case a visit or contact took place after the efficacy cut-off. (An event might be excluded from the analysis in case the event occurred before the Efficacy Cut-off but was reported after the Efficacy Cut-off and it was not possible to adjudicate the event before data base closure). Subjects will be kept in the study group to which they were randomized and the follow-up period for each subject will be as long and complete as possible. This ITT data scope will be applied to the primary analysis of the primary and secondary efficacy variables and safety variables.

Data scope according to treatment (on-treatment)

The on-treatment data scope will include all outcome events observed from randomization until 2 days following permanent discontinuation of the study drug.

Analyses according to the on-treatment data scope will be based on the safety analysis set (see section 5.1.2).

This on-treatment data scope will be applied to the supportive analysis of the primary and secondary efficacy variables and safety variables.

4.5.3 Censoring rules for time-to-event variables

For any time-to-event variable in this study, the following censoring rules will be applied:

Censoring rules for analyses according to the intention-to-treat principle

For analyses according to the intention-to-treat principle, randomized subjects without documentation of an event will be censored at

- the subject's EOT visit if the subject attends the EOT visit within the Trial close-out window,
- the subject's date of last contact prior to efficacy cut-off date if (a) the subject does not attend his/her EOT visit within the Trial close-out window and (b) the subject's date of last trial contact is not after the efficacy cut-off date,
- the common efficacy cut-off date if (a) the subject does not attend his/her EOT visit within the Trial close-out window and (b) the subject's date of last trial contact is after the efficacy cut-off date.

This censoring rule will be applied to all analyses according to the intention-to-treat principle. In the rare event that for a subject only survival status information can be retrieved at the end of the study but no information on other outcomes, the last follow-up / trial contact where survival status information was obtained will still be used to determine the censoring date for the subject and if there were no known events up to then the subject will be considered as event-free.

Censoring rules for on-treatment analyses

For on-treatment analyses, all randomized subjects with at least one dose of study medication and without documentation of an event within the on-treatment data scope will be censored at the date of last double-blind dose of antithrombotic study treatment + 2 days.

Note that if a subject stops treatment at the EOT visit and experiences an event up to 2 days thereafter, the event will be counted in this analysis but not in the primary analysis.

4.6 Determination of sample size

The study is event-driven and it is estimated that 7000 patients (3500 per treatment group) need to be randomized in order to have approximately 450 patients experiencing a confirmed primary efficacy outcome event using the ITT data scope. This number of events will allow the demonstration of superiority of rivaroxaban compared to ASA with regard to the primary outcome with a power of 90% and a one-sided level of significance $\alpha=0.025$ under the following assumptions:

- An average yearly event rate of the composite primary efficacy outcome of 3.8% in the ASA group (4.0% for patients with age ≥ 60 years, 2.0% for 10% of patients with age < 60 years)
- Effect size: A 30% RRR for stroke and systemic embolism in the rivaroxaban group compared to ASA
- Length of the recruitment period is 2 years and the total study duration is 3 years
- Approximately 10% of patients will permanently discontinue study medication in the first year and 7% in following years
- Approximately 5% of patients with a diagnosis of AF will switch to standard treatment during study conduct
- Approximately 3% patient deaths per year and 1% of patients lost to follow-up per year

Under these assumptions the expected RRR to be observed in this study would be 26% for the primary efficacy outcome.

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

Sample size estimation was based on a Statistical Analysis Software (SAS) macro provided by [Shih \(1995\)](#).

5. Analysis Sets

5.1 Assignment of analysis sets

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

5.1.1 Intention-to-treat analysis set (ITT)

The intention-to-treat analysis set, also termed full analysis set in the International Conference on Harmonization (ICH) E9 guideline, will include all randomized subjects.

5.1.2 Safety analysis set (SAF)

The safety analysis set will include all randomized subjects who received at least one dose of study medication.

6. Statistical Methodology

6.1 Population characteristics

6.1.1 Disposition

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

- Study sample sizes (subjects enrolled, randomized, and valid for Safety analysis set) by region and country
- Study sample sizes by country and site
- Subject disposition
- Number of subjects and primary reasons for screening failures (only overall)
- Number of subjects and primary reasons for permanent discontinuation of study medication (by treatment group and overall for ITT and SAF)
- Number of subjects and primary reasons for discontinuation of study follow-up (by treatment group and overall for ITT and SAF)
- Number of subjects withdrew consent as well as Lost to Follow-up

Kaplan-Meier plots will be used to show:

- Time from randomization to last study medication,
- Time from randomization to last contact prior to efficacy cut-off,
- Time from randomization to last trial contact

by treatment group and overall for ITT and SAF.

6.1.2 Demographics

Demographic variables and baseline characteristics will be summarized by treatment group and overall in the ITT and SAF. Summary statistics will be presented for metric variables. Frequency tables will be presented for categorical variables.

Demography includes age, gender, race, ethnicity, region (North America; South America; Western Europe; Eastern Europe; Asia), body height, body weight, body mass index (BMI) and smoking history. Age, body weight and BMI will each be given as continuous variable and categorized with the following categories:

- Age: <60; 60-75; >75 years (for publication: <75; ≥75 years)
- BMI: < 25; ≥ 25 to < 30; ≥ 30kg/m² (for publication: < 30; ≥ 30kg/m²)

- Weight: <70; 70-90; >90 kg (for publication: <50; 50-100; >100 kg)

The following additional baseline characteristics will be analyzed:

- Sex: male; female
- Race: White; Black; Asian; other
- Region: North America; South America; Western Europe; Eastern Europe; Asia
- eGFR: <50; 50-80; >80 mL/min
- Stroke or TIA prior to index event: yes or no
- Time from index stroke to randomization: ≤ 30 days; 30 days to 3 months; > 3 months
- Presence of patent foramen ovale: present or absent / not known
- Cardiac rhythm monitoring: <48; ≥ 48 hours
- Hypertension: yes or no
- Diabetes: yes or no
- Heart failure: yes or no
- Tobacco use: never, former, current

6.1.3 Medical history

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

Medical history findings will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes. Medical history will be presented for each MedDRA Primary System Organ Class (SOC) and Preferred Term (PT) by treatment group and overall based on ITT.

6.1.4 Protocol Deviations

A summary of major protocol deviations will be given by frequency tables showing the number of subjects with major protocol deviations overall, by type of deviation. Analysis will be based on ITT.

Types of major protocol deviations include:

- Significant inclusion criteria not fulfilled
- Significant exclusion criteria fulfilled
- Failure to obtain informed consent before initiation of study procedures
- Prohibited medication Failure to report SAE
- Failure to report outcome event
- Other safety

6.1.5 Prior and Concomitant Medications

Frequency tables by type of medication will be provided for prior medications prior to stroke (for antiplatelets and anticoagulants) and prior to randomization (for all) and separately for concomitant medication at 6 month, at EOT, and pooled. Analyses will be by treatment group and overall based on ITT.

Prior and concomitant medications will be coded by Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization Drug Dictionary (WHO-DD) using the version as outlined in the Trial Summary (TS) domain.

6.1.6 Extent of Exposure and Compliance

All analyses related to intake of study medication will be by treatment group and overall based on SAF.

The treatment duration will be calculated (date of last study medication- date of first study medication+1 day) and analysed descriptively. Additionally the number of subjects by treatment duration category will be given. Categories (3 months, 6 months, 9 months, 12 months, 18 month, 24 month) will include all subjects with at least XX months treatment duration.

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

The number of tablets taken will be calculated (tablets dispensed-tablets returned) and analysed descriptively, as well as corresponding extent of exposure (number of tablets taken*dose).

Compliance will be presented by visit as entered in the CRF and summarized for the whole study. The number of subjects with at least 80% compliance will be presented.

6.2 Efficacy

6.2.1 Primary efficacy variable

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

- Stroke (ischemic, hemorrhagic, and undefined stroke, TIA with positive neuroimaging)
- Systemic embolism

6.2.2 Secondary efficacy variables

The secondary efficacy variables of this study are the time from randomization to first occurrence of:

- Cardiovascular death (including death due to hemorrhage), recurrent stroke, systemic embolism, and MI
- All-cause mortality
- Individual components of the primary and secondary efficacy outcomes (stroke, CV death, and MI) as well as ischemic stroke, and disabling stroke (modified Rankin score 4 and 5)

These are listed in the order of sequential testing.

6.2.3 Subgroup variables

The following subgroup analyses based on baseline demographics are planned for the comparison of the primary efficacy and safety outcomes:

- Age: <60; 60-75; >75 age (for publication: <75; ≥ 75 years)
- Sex: male; female
- Race: White; Black; Asian; other
- Region: North America; South America; Western Europe; Eastern Europe; Asia
- BMI: < 25; ≥ 25 to < 30; $\geq 30\text{kg/m}^2$ (for publication: < 30; $\geq 30\text{kg/m}^2$)
- Weight: <70; 70-90; >90 kg (for publication: <50; 50-100; >100 kg)
- eGFR: <50; 50-80; >80 mL/min
- Stroke or TIA prior to index event: yes or no
- Time from index stroke to randomization: ≤ 30 days; 30 days to 3 months; > 3 months
- Presence of patent foramen ovale: present or absent / not known
- Cardiac rhythm monitoring: <48; ≥ 48 hours
- Hypertension: yes or no
- Diabetes: yes or no

Higher absolute efficacy event rates are expected for the following subgroups: older age, females, renal impairment, stroke or TIA prior to index event, hypertension, and diabetes. Even though rivaroxaban has not been tested in patients with ESUS, based on earlier studies with rivaroxaban a consistent (relative) treatment effect across all of the planned subgroups is expected.

A limited number of additional subgroup analyses may be proposed by the Steering Committee.

The randomization was stratified by the dichotomic age group variable for age below 60 years (No/Yes) and by country.

6.2.4 Analysis of the primary efficacy variable

The primary analysis will include events as adjudicated by the ICAC and will be based on the ITT analysis set using the ITT data scope.

In order to evaluate whether rivaroxaban is superior to ASA in prolonging the time to a primary efficacy (PE) outcome event in patients with ESUS, the following null hypothesis (H_0) will be tested at the significance level of 0.025:

$H_{0, PE}$: $S_R(t) = S_A(t)$ for all time points $t \geq 0$, (i.e. “there is no difference between the rivaroxaban treatment group and the ASA control group regarding the primary efficacy outcome for all time points”)

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 and S_A denotes the survival function of the ASA group.

The following decision rule to test the null hypothesis will be applied:

According to the size of this study, it is justified to assume under $H_{0, PE}$ a sufficiently close approximation of the one-sided stratified (according to dichotomic age group) log-rank test to the normal distribution. If the z-value from the one-sided log-rank test (for the difference $S_R(t) - S_A(t)$ with stratification) is larger than the critical quantile from the normal distribution ($z_{0.975} = 1.96$), the null hypothesis will be rejected in favor of the alternative hypothesis.

Kaplan-Meier estimates of cumulative risk and Nelson-Aalen estimates of the 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.

To derive the log-rank Z test statistic and the variance V of the log-rank statistics, SAS program code corresponding to the following will be used:

```
PROC LIFETEST DATA = <dataset> ALPHA=0.05 METHOD=KM NELSON;  
  STRATA stratumn;  
  TEST trtgrp;  
  TIME ttevalue * ttecnsr(0);  
RUN;  
  
/*  
where  
dataset = name of sub-dataset including all ITT subjects randomized  
trtgrp = variable coding randomized treatment group  
ttevalue = time to first occurrence of primary efficacy outcome event  
ttecnsr = censoring index (0 = right-censored, 1 = event)  
stratumn = variable for stratification factor (age group with two levels)  
*/
```

Hazard ratio and corresponding two-sided 95% confidence intervals will be estimated based on an age-group stratified Cox proportional hazards models. 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. Censoring will be assumed independent of the treatment group assignment.

For the analysis of the primary outcome in this study, the hazard function $h(t)$ is the chance that an individual experiences an event of the primary efficacy outcome in the next instant in time, given that the individual has not had such an event up to time t . For example, for the comparison of rivaroxaban with ASA (control), the corresponding stratified Cox proportional hazards model can be described by the following equation:

$$h_k(t, x_i) = h_{0k}(t) \exp(\beta x_i),$$

where

$h_k(\cdot)$ hazard function for primary efficacy outcome for stratum k , $k = 1, 2$ (k represents age group stratification factor), as a function of time and subject's covariates

$h_{0k}(\cdot)$ unspecified underlying baseline hazard function for primary efficacy outcome per stratum k ; hazard of an individual with $x_i = 0$

t time (in days) relative to the randomization date

x_i treatment group of subject i

β unknown parameter (to be estimated); hazard ratio = $\exp(\beta)$

SAS program code corresponding to the following will be used:

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

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

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

Subjects without a primary efficacy outcome event will constitute a right-censored observation (see section 4.5.3 for censoring rules). Primarily, for the time-to-event analysis the censoring mechanism will be assumed to be non-informative. Additional sensitivity analyses will be performed in order to evaluate the robustness of the statistical results under different assumptions (see section 6.2.7).

6.2.5 Analysis of secondary efficacy variables

A single primary efficacy outcome will maintain strict control of the type I error rate. If the primary efficacy outcome is statistically significant, the secondary efficacy outcomes will be tested in a sequential manner according to the order as listed in section 6.2.2.

If the superiority of rivaroxaban for the primary outcome is declared, the following alternative hypotheses, superiority of rivaroxaban compared with ASA for the secondary efficacy outcomes will be tested in the sequential order. That is, the subsequent ordered secondary outcome will be tested only if superiority can be shown for the previous outcomes.

If an individual test during any step is not statistically significant, further testing may continue but significance will not be claimed. This hierarchical testing procedure will control the global Type 1 error level.

The primary analysis of the secondary variables will include events as adjudicated by the ICAC and will be based on the ITT analysis set using the ITT data scope.

The first secondary efficacy variable (SE1) of this study is the time from randomization to first occurrence of cardiovascular death (including death due to hemorrhage), recurrent stroke,

systemic embolism, or MI. The following null hypothesis will be tested at the significance level of 0.025:

$$H_{0, SE1}: S_{R1}(t) = S_{A1}(t) \text{ for all time points } t \geq 0,$$

The one-sided alternative hypothesis will be:

$$H_{1, SE1}: S_{R1}(t) > S_{A1}(t) \text{ for at least one time point } t \geq 0, \text{ and } S_{R1}(t) \geq S_{A1}(t) \text{ for all time points } t \geq 0,$$

where S_{R1} denotes the survival function of the rivaroxaban and S_{A1} denotes the survival function of the ASA group.

The second secondary efficacy variable (SE2) of this study is the time from randomization to first occurrence of death from any cause. The following null hypothesis will be tested at the significance level of 0.025:

$$H_{0, SE2}: S_{R2}(t) = S_{A2}(t) \text{ for all time points } t \geq 0,$$

The one-sided alternative hypothesis will be:

$$H_{1, SE2}: S_{R2}(t) > S_{A2}(t) \text{ for at least one time point } t \geq 0, \text{ and } S_{R2}(t) \geq S_{A2}(t) \text{ for all time points } t \geq 0,$$

where S_{R2} denotes the survival function of the rivaroxaban and S_{A2} denotes the survival function of the ASA group.

The analysis methods will be those described for the primary efficacy outcome.

The same analysis will be performed for the individual components of the primary and secondary efficacy outcomes (stroke, CV death, and MI) as well as ischemic stroke, and disabling stroke (modified Rankin score 4 and 5).

6.2.6 Subgroup analysis

Subgroup analyses for the efficacy and safety outcomes will be performed based on the same analysis sets and data scopes as in the main analyses of the study outcomes. The subgroup analyses will be presented descriptively without formal hypotheses testing.

Homogeneity of treatment effect in subgroups, both in magnitude and direction, will be assessed by adding a covariate for the subgroup variable and the corresponding treatment-subgroup interaction to the respective (age-group stratified) Cox proportional hazards model used in the main analysis. Additionally the hazard ratio for the treatment effect will be estimated separately within each level of a subgroup variable using the same Cox proportional hazards.

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

6.2.7 Sensitivity analyses (for regulatory submission)

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

The analysis of the primary and secondary efficacy variables as described in section 6.2.4 and 6.2.5 will be repeated based on the safety analysis set using the on-treatment data scope.

The analysis of the primary and secondary efficacy variables as described in section 6.2.4 and 6.2.5 will be repeated counting outcome events as reported by the investigators.

The analysis of the primary and secondary efficacy variables as described in section 6.2.4 and 6.2.5 will be repeated using the Cox proportional hazard model without stratification.

Despite all efforts it will be hard to completely avoid loss to follow-up within this study (White).

The robustness of the primary study result will be evaluated in a sensitivity analysis accounting for non-compliance to study follow-up, i.e. accounting for missing data with regard to events and person-time between the date of loss to follow-up and the Efficacy cut-off date

The analysis will:

- Estimate the hazard at time of time of loss to follow-up, adjusting for observed covariates
- Inflate the hazard only in the Rivaroxaban group by a known factor; assumes non-informative censoring in the control group
- Impute events to the end of the study 1,000 times, assuming exponential distribution; combine using standard multiple imputation combining rules
- Increase the inflation factor until upper limit of two-sided 95% confidence interval crosses 1.0; this will be the “tipping point”

The higher the tipping point the more robust the study result with regard to missing data.

6.3 Pharmacokinetics / pharmacodynamics

Not applicable

6.4 Safety

6.4.1 Adverse events

Adverse events (AEs) will be coded by MedDRA. The version number of MedDRA used for the analyses will be stored in the clinical database/system set-up. A listing will be provided linking the original investigator terms and the coded terms.

Analyses of reported adverse events will be performed based on the safety analysis set and all data scopes as outlined in section **Error! Reference source not found.**

In case of uncertainty (e.g., missing or incomplete dates), adverse events will be classified as “treatment emergent” following the worst case approach.

An overall summary of AEs and treatment-emergent (TE) AEs will be generated by treatment group and overall.

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

Serious adverse events (SAEs), AEs leading to discontinuation and AEs of particular concern will be listed. The date, relative day (to study medication) and phase of the study (pre-treatment, during treatment, post-treatment) will be included.

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

6.4.2 Primary safety variable

The primary safety variable is the time from randomization to time of first occurrence of a major bleeding (ISTH) defined as a bleeding event that meets at least one of the following criteria:

- Fatal bleeding, and/or
- Bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), and/or

- Clinically overt bleeding associated with a recent decrease in the hemoglobin level of more or equal than 2 g/dL (20 g/L; 1.24 mmol/L) compared to the most recent hemoglobin value available before the event, and/or
- Clinically overt bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood

6.4.3 Secondary safety variables

The secondary safety variables are the time from randomization to time of first occurrence of:

- Life-threatening bleeding, defined as a subset of major bleeding that meet at least one of the following criteria:
 - Fatal bleeding
 - Symptomatic intracranial bleeding
 - Reduction in hemoglobin of at least 5 g/dl (50 g/l; 3.10 mmol/L)
 - Transfusion of at least 4 units of packed red cells or whole blood
 - Associated with hypotension requiring the use of intravenous inotropic agents
 - Necessitated surgical intervention
- Clinically relevant non-major bleeding, defined as non-major overt bleeding but
 - Requires medical attention (e.g., hospitalization, medical treatment for bleeding), and/or
 - Is associated with a study drug interruption of more than 14 days.
- Intracranial hemorrhage

6.4.4 Other safety variables

All bleeding events will be analyzed. In addition to the analysis according to ISTH as described above, bleeding events will be analyzed according to GUSTO, TIMI and BARC definitions.

Vital signs and weight will be analyzed descriptively.

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

6.4.5 Analysis of safety variables

The primary analysis of the safety variables will be based on the ITT analysis set using the ITT data scope. Additionally the safety variables will be analyzed based on the safety analysis set using the on-treatment data scope.

The primary and secondary safety variables will be tested parallel without control of the type I error level.

In order to evaluate whether rivaroxaban is different to ASA with respect to the time to a bleeding event in patients with ESUS, the following null hypothesis will be tested at the two-sided significance level of 0.05:

$$H_{0, B}: S_{RB}(t) = S_{AB}(t) \text{ for all time points } t \geq 0,$$

The two-sided alternative hypothesis will be:

$$H_{1, B}: S_{RB}(t) \neq S_{AB}(t) \text{ for at least one time point } t \geq 0,$$

where S_{RB} denotes the survival function of the rivaroxaban and S_{AB} denotes the survival function of the ASA group.

The analysis methods will be those described for the primary efficacy outcome.

The safety variables will be analyzed by subgroup as describe for the efficacy variables.

6.5 Other procedures and variables

The analysis of other variables will by treatment group and overall and based on ITT.

Other variables are:

- Healthcare Resource Use
 - hospitalizations (total days length of stay, intensive care unit/cardiac care unit days, ward type); emergency room visits; unscheduled outpatient physician consultations; or visits related to bleeding, surgeries, other selected procedures (inpatient and outpatient); and post-stroke care (status of care, home health or rehabilitation center or long term care). Days off-work.
- European Quality of Life-5 Dimensions (EQ-5D)
 - EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Assessments will be done using both a descriptive system and the subject's self-rated health on a visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'.

The following variables are of interest:

- EQ-5D single dimensions

- EQ-5D Visual Analogue Scale (VAS) values
- EQ-5D index score
- Montreal Cognitive Assessment (MoCA)
 - The Montreal Cognitive Assessment (MoCA) test assesses several cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. For each task correctly completed, one point is assigned. All subscores are summed up and adjusted for individuals with ≤ 12 years education to derive a total score ranging between 0 (for a totally cognitive impaired subject) and a maximum of 30 points (cognitively healthy participant).
- Digit Symbol Substitution test (DSS)
 - The DSS test is a neuropsychological test sensitive to brain damage, dementia, age and depression. It consists of nine digit-symbol pairs followed by a list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (120 sec) is measured.
- Standard Assessment of Global-Activities in the Elderly (SAGE)
 - The SAGE questionnaire comprises 15 items, each describing an activity for which the respondent has to indicate how much difficulty the subject has encountered in performing this activity in the past month. Regarding scoring for an item, 0 points are assigned if the participants endorse the “None/never performed” response, 1 point to the “Mild” response, 2 points to the “Moderate” response, and 3 points to the “Severe” response. One additional point will be assigned when in response to question 11, 12, and 15 the respondent declares the need for help from another person or a tool to walk, jump the stairs or to bath. The total score will range from 0, describing a very independent participant over a broad spectrum of activities, to 48, describing a very dependent subject.
- Modified Rankin Score

6.6 Net clinical Benefit

The benefit-risk of rivaroxaban vs aspirin will be evaluated based on the excess number of events between treatments for events intended to be prevented (benefits) and events that may be caused (risks). Excess number of events is defined as the difference in event rate times a hypothetical population size (eg, 10,000 patients). To have a comprehensive benefit-risk evaluation, several comparisons will be considered.

The first measure of net clinical benefit in this study is the primary efficacy outcome. Although named efficacy outcome it includes not only thrombotic events, but also hemorrhagic events (hemorrhagic stroke).

The second measure of net clinical benefit is all-cause mortality.

As an overall valid measure of net clinical is hard to be defined, a variety of measures will be presented side by side to allow weighting positive effects and harms. For the efficacy these will include the thrombotic events of the primary and secondary efficacy endpoints. For the safety side these will include the hemorrhagic events of the efficacy endpoint, ISTH major bleeding, life-threatening bleeding, and intracranial hemorrhage.

Other measures may be added as they may help to assess the net clinical benefit.

7. Document history and changes in the planned statistical analysis

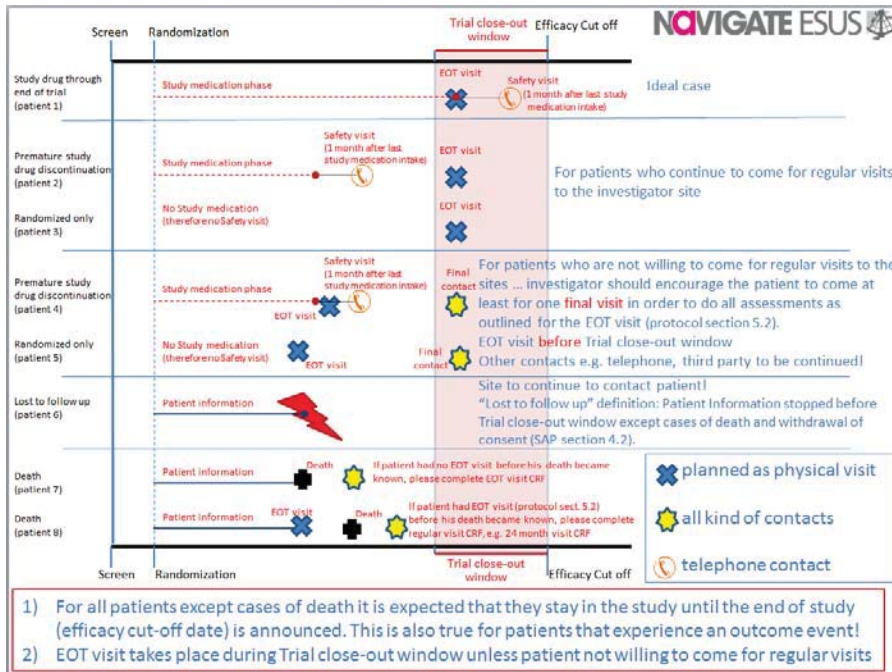
- Draft SAP dated 30 Sep 2014
- Second SAP draft for team review dated 10 Nov 2014
- Proposed final SAP for team review dated 14 Jan 2015
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8. References

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Appendix A: Patient follow-up



Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS), comparing rivaroxaban 15 mg once daily with aspirin 100 mg (NAVIGATE ESUS)

Secondary prevention of stroke in patients with a recent ESUS

Bayer study drug BAY 59-7939/rivaroxaban

Clinical study phase: III **Date:** 20 December 2017

Study No.: 16573 **Version:** 3.0

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

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Abbreviations

AE	Adverse event
AF	Atrial fibrillation
APCC	Activated prothrombin complex concentrate
ARISTOTLE	Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE)
ASA	Acetylsalicylic acid; aspirin
AVERROES	A Phase III Study of Apixaban in Patients With Atrial Fibrillation (AVERROES)
BHC	Bayer HealthCare
b.i.d.	Twice daily
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence interval
ConMed	Concomitant medication
CRO	Contract research organization
CSR	Clinical Study Report
CT	Computed tomography
cTn	Cardiac troponin
CV	Cardiovascular
CYP3A4	Cytochrome P450 isoenzyme 3A4
DSS	Digit Symbol Substitution test
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
e.g.	for example
eGFR	Estimated glomerular filtration rate
ENGAGE	Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (EngageAFTIMI48)
EOT	End-of-treatment
EQ-5D	European Quality of Life-5 Dimensions questionnaire
ESUS	Embolic stroke of undetermined source
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
H	Hypothesis
HDPE	High-density polyethylene
HEOR	Health Economics, Outcomes & Reimbursement
HR	Hazard ratio
ICAC	Independent Central Adjudication Committee
ICF	Informed consent form
ICH	International Conference on Harmonisation
IB	Investigator's brochure
i.e.	id est (that is)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	International ratio
IRB	Institutional Review Board
ISAC	Independent Statistical Analysis Centre

ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-to-treat
IxRS	Interactive web/voice response system
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
Mo	Month
MoCA	Montreal Cognitive Assessment
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Score
NSAID	Non-steroid anti-inflammatory drug
NV	Corporation (in The Netherlands)
NVAF	Non-valvular atrial fibrillation
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
o.d.	Once daily
OMP	Ortho McNeil Pharmaceuticals
p	p-value
PCC	Prothrombin complex concentrate
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
P-gp	P-glycoprotein
PICCS	Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS)
PID	Patient identification
PPS	Per protocol set
PT	Prothrombin time
PV	Pharmacovigilance
QA	Quality assurance
RRR	Relative risk reduction
S	Survival
SAE	Serious adverse event
SAF	Safety set
SAGE	Standard Assessment of Global-Activities in the Elderly
SAP	Statistical analysis plan
SMQ	Standardised MedDRA Query
SC	Steering Committee
SUSAR	Suspected unexpected serious adverse reaction
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
TTE	Transthoracic echocardiogram
USA	United States of America
V	Visit
VKA	Vitamin K antagonist
vs.	versus
VTE	Venous thromboembolism
WARSS	Warfarin-Aspirin Recurrent Stroke Study
WHO	World Health Organization
WMH	White matter hyperintensities

1. Introduction - amended

Globally, cerebrovascular disease (stroke) is the second leading cause of death and the fourth leading cause of disease burden as measured in disability-adjusted life years. The World Health Organization (WHO) estimates that worldwide 16 million people suffer a first ever stroke annually, with 5 million deaths due to stroke in 2005, and another 5 million left permanently disabled.

Recently, the concept of “embolic stroke of undetermined source” (ESUS) has developed, recognizing that except for lacunar strokes, most cryptogenic strokes are embolic. The sources of embolism underlying ESUS include the heart (either within the heart or via paradoxical embolism from a venous source), aortic arch, or the large cervical and cerebral arteries.

Randomized clinical trials have addressed secondary prevention for all major ischemic stroke subtypes except for cryptogenic stroke or ESUS. Among the estimated 300,000 patients with acute cryptogenic stroke annually in North America and Europe there has been little progress in secondary prevention during the past two decades. There is a substantial unmet medical need in this patient population, as despite treatment with antiplatelets, the recurrent stroke rate still remains at 3 to 6% annually.

There is persuasive evidence that the dominant underlying pathophysiology of ESUS is embolism (cardioembolic, arteriogenic, or paradoxical). Improvements in imaging technology and an increased appreciation of the underlying pathophysiology of ESUS have resulted in better understanding and in a practical clinical definition of ESUS so that these patients can be reliably identified.

Based on evidence for superior efficacy of warfarin anticoagulation over ASA for other types of embolic stroke, anticoagulation is expected to be superior to ASA in ESUS patients. The direct oral Factor Xa-inhibitor rivaroxaban, when compared with VKAs, has been demonstrated to be effective against embolic stroke related to non-valvular AF. Because of its predictable anticoagulant activity and low risk of intracranial hemorrhage, it is expected that rivaroxaban will reduce stroke recurrence in ESUS compared with ASA, and with an acceptable safety (bleeding) profile. Rivaroxaban has also been shown to be efficacious for the treatment of DVT and PE, prevention of recurrent DVT and PE, prevention of VTE following total hip and total knee replacement, and also for prevention of atherothrombotic events after an acute coronary syndrome with elevated cardiac biomarker. Rivaroxaban has no dietary restrictions and only few drug interactions and does not require routine coagulation laboratory monitoring.

Given these considerations, a large, multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study comparing rivaroxaban 15 mg o.d. with

ASA 100 mg o.d. for the secondary prevention of stroke and prevention of systemic embolism will be conducted.

The IDMC recommended on October 2, 2017 that the NAVIGATE ESUS trial be stopped: “In the absence of offsetting benefit, and little chance of showing benefit if the study were completed, there is a clear risk of excess bleeding.” There was an increase in ISTH-defined major hemorrhage in the rivaroxaban arm that was not unexpected. However there was no offsetting benefit in reduction of stroke. Futility analysis showed <1% likelihood of demonstrating a substantial benefit for stroke prevention if the trial were continued to the planned termination in 2018. The Executive Operations Committee carefully reviewed the results and accepted the DMC recommendation to close the trial. All investigators and responsible Health Authorities were informed about the stop of the study on October 5, 2017.

This core SAP is based on the Clinical Study Protocol BAY 59-7939/16573 amendment version 2.0 from 5 November 2015 and contains definitions of analysis sets, key derived variables and statistical methods for analysis of efficacy and safety for the ESUS study. It provides a technical and detailed elaboration of the principal features of the planned analyses, e.g., censoring schemes for time-to-event variables. Amendments and/or appendices to this core SAP may be used to provide more details on the coding guidelines, data-handling, and output tables and figures.

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

2. Study Objectives

The primary efficacy objective is:

- To evaluate whether rivaroxaban is superior to aspirin in reducing the risk of recurrent stroke and systemic embolism in patients with a recent ESUS

The secondary efficacy objective is:

- To evaluate whether rivaroxaban is superior to aspirin in reducing the risk of cerebrovascular events, cardiovascular events, and mortality in patients with a recent ESUS

The safety objective is to document the incidence of clinically relevant bleeding.

3. Study Design

This is a multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study in patients with a recent ESUS.

Following provision of informed consent, patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomly allocated by an interactive voice/web response

system (IxRS) to either rivaroxaban 15 mg o.d. or ASA 100 mg o.d. in a 1:1 ratio. No dose adjustment will be made for patients with mild or moderate renal impairment.

Patients may be randomized and receive the first study medication intake between 7 days and 6 months after the qualifying stroke event. In case of minor strokes (National Institutes of Health Stroke Score [NIHSS] ≤ 3), study medication may be initiated as early as 3 days after stroke onset if all eligibility assessments have been completed. In the presence of hemorrhagic transformation on the qualifying brain imaging study or if intravenous thrombolysis therapy was given for the qualifying stroke, study medication will not be initiated before 10 days after the acute stroke event unless a repeat CT or magnetic resonance imaging (MRI) performed before randomization documents the absence of new or extension of hemorrhage.

Patients will be enrolled as early as possible after the required diagnostic evaluation is complete and eligibility criteria are fulfilled. The goal is that the majority of patients are enrolled within 3 months, and fewer patients between 3 and 6 months.

Randomization will be stratified by country and age <60 and ≥ 60 years. Patients < 60 years will need to have at least one risk factor such as stroke or TIA (includes covert/silent strokes on neuroimaging) prior to qualifying stroke, diabetes, hypertension, current tobacco smoker or heart failure.

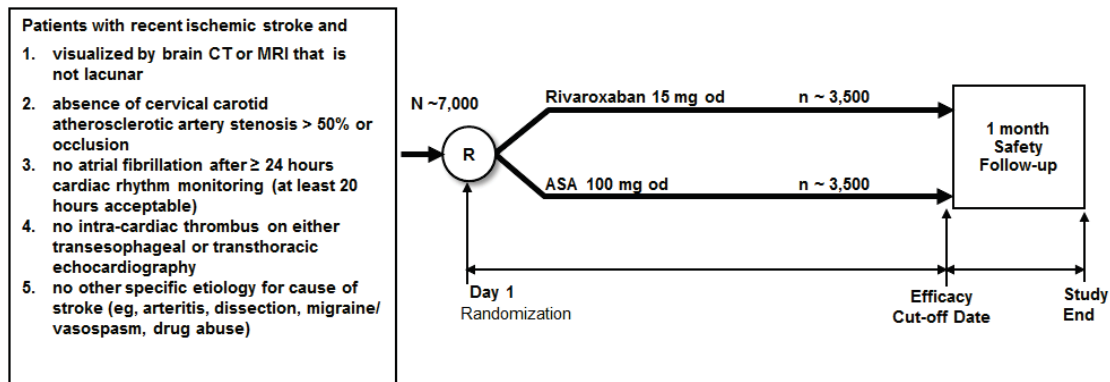
At randomization, patients will receive study medication and instructions for its administration. Thereafter, patients will return to the clinic at 1, 6, and 12 months and then every 6 months until the end of study (efficacy cut-off date) is announced. At 3 months, the patient will be contacted by telephone. Throughout the study and at clinic visits, patients will be assessed for efficacy (stroke, systemic embolism, MI, CV death, or all-cause mortality) and safety (vital signs, bleeding, serious adverse events [SAEs] which are not outcome events, non-serious adverse events [AE]s leading to permanent discontinuation of study treatment, and any non-serious AEs of particular concern to the investigator).

The trial will continue until approximately 450 patients are anticipated to have experienced a positively adjudicated primary efficacy outcome event. This is anticipated to occur approximately 3 years after the first patient is randomized, but may vary depending on the recruitment rate as well as the primary event rate. A telephone safety visit will be performed 1 month after the end-of-treatment (EOT) visit.

Patients permanently discontinuing study treatment will continue to be followed, and outcome events and vital status must be assessed in these patients until the end of the study via either clinic visits or telephone contacts.

All efficacy and safety analyses are based on time from randomization to time of first event. Suspected clinical study outcomes will be assessed by the ICAC, which will be blinded to treatment allocation. Adjudicated results will be the basis for the final analyses. The IDMC will monitor patient safety during the study and give recommendations to the SC and sponsor.

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



The target patient population comprises patients with a recent ESUS. These patients have substantial risk for recurrent stroke and other thromboembolic events despite antiplatelet therapy, the current standard of care. A double-blind, randomized trial design comparing rivaroxaban with ASA is deemed the most appropriate design to allow for an unbiased evaluation of rivaroxaban as a treatment option for this patient population in an international trial.

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 final efficacy outcome event has been adjudicated for patients from all participating clinical sites (EU and non-EU).

4. General Statistical Considerations

4.1 General Principles

All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data, as appropriate. Frequency tables will be generated for categorical data. The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

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

An excessive rate of patient discontinuations from either treatment or study follow up may render the trial non-interpretable. In this study, outcome events and vital status data will be collected until the end of the study, even if patients are no longer taking study medication.

This means that clinical data from all randomized patients will be collected at trial close-out as far as possible.

A subject who signed an informed consent form, and, for any reason (e.g., failure to satisfy the in- and exclusion criteria) terminates the study without being randomized is regarded as a “screening failure”.

A randomized subject who permanently discontinues study treatment before their End of treatment Visit for any reason is defined as having had a permanent discontinuation of study medication (including subjects who were randomized but never started taking any study medication). The reason for permanent discontinuation of study medication will be collected.

For subjects who permanently discontinue study medication, different options of follow-up will be discussed to collect outcome events and vital status. This can include regular study visits, regular phone calls with the patient or otherwise with the general practitioner or family relative, or a contact at the end of the study. Patients who do not agree to attend regular study visits the investigator will encourage to come to at least one final visit to perform assessments to the greatest extent possible as outlined for the End of treatment Visit.

However, all randomized subjects will be encouraged to remain on study treatment and under observation for the full duration of the study. Discontinuation of study treatment is not the equivalent to withdrawal of informed consent. In cases where subjects indicate they do not want to “continue”, investigators must determine whether this refers to discontinuation of study treatment, unwillingness to attend follow-up visits, unwillingness to have telephone contact, unwillingness to have any contact with study personnel, or unwillingness to allow contact with a third party (e.g., family member, doctor). Every effort will be made to continue to follow the subject and survival status information must be determined for all subjects at the end of the study. The expectation is that only very few subjects will have incomplete follow-up (in any form) within this trial.

A subject will be declared to have incomplete follow-up or to be lost to follow-up (i.e., to be completely non-compliant to follow-up) if, despite of all possible efforts, all investigators, dedicated site staff, and/or PHRI Project Office (as applicable and as local regulations allow) are not able to contact the subject or a third party (e.g., family member, doctor). Every possible effort will be made to contact the subject or a third party and to determine the endpoint and survival status and reason for discontinuation as local law permits. If it is documented in the database that the subject is alive at the end of the study, the subject will not be classified as lost to follow-up, but as alive.

4.3 Handling of Missing Data

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

Missing or incomplete event dates

When an event date is not known, the site investigator will be asked to provide a best estimate as to when the event occurred. Even though the exact date of an event is unknown, the investigator often does know some information that would indicate the approximate date, such as the first week of a month, in the fall of a year, or the middle of a particular year, or at least the date when the subject was last seen or contacted. This information can be meaningfully incorporated into the estimated date recorded, as this is likely to be closer to the true date than any produced by an uninformed computer program. This estimated date should be the middle date within the period that the event is known to have occurred. If the event is known to have occurred in the first week of a month, then the date in the middle of that week should be recorded as the estimate. If it occurred in the fall of a year, then the middle date in the fall is the appropriate estimate. If no information is known then the date in the middle of the plausible time period should be given, based on the last contact with the subject prior to the event (start date of plausible time period) and the date of contact when information about the event was known (end date of plausible time period). This method for date estimation has been used in many studies and is recommended by Dubois.

If the date/time information is not sufficient to determine whether an event occurred prior or after randomization, the event is considered as an outcome, to be conservative. The event start date will be imputed no earlier than randomization date.

4.4 Interim Analyses and Data Monitoring

The IDMC will monitor the study for efficacy and for safety by reviewing unblinded event rates.

There will be 2 formal interim analyses to assess efficacy, which will occur when approximately 50% and 67% of the planned primary efficacy events have accrued. The IDMC may recommend early study termination at these interim analyses, if there is overwhelming superiority of rivaroxaban for efficacy ($Z > 4$, i.e. a reduction of 4 standard deviations in the analysis of the primary efficacy outcome at interim analysis). 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 over ASA.

The IDMC has the flexibility to initiate further interim analyses after the first formal efficacy analysis at 50%, if deemed appropriate. Given the conservative nature of the monitoring guidelines used in this trial, no adjustment of the significance level for the final analysis is required.

The execution of the interim analyses and decision rules will be specified in the IDMC charter.

All (unblinded) statistical analyses for the IDMC and the interim analysis will be performed by the ISAC (Independent Statistical Analysis Centre).

The steering committee will review overall blinded event rates to ensure that they meet protocol projections. If overall event rates are lower than expected, consideration will be given to altering the trial design, such as increasing the sample size or extending the study duration without knowledge of any treatment effect.

4.5 Data Rules

4.5.1 Analysis Dates - amended

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

- Efficacy cut-off date:
The efficacy cut-off date is the 5th of October 2017, the date the early stopping of the trial was officially announced.
- Trial close-out window:
The Trial close-out window is the time period when all subjects are to return to the clinic for an End of treatment Visit.

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

- Randomization date:
The date of randomization to antithrombotic study treatment of the subject.
- End of treatment (EOT) Visit date:
This is the date of the EOT Visit for the individual subject.
After the announcement of the end of the study, all subjects are to return to the clinic for their EOT Visit within the pre-specified window (Trial close-out window).
If subjects do not have an EOT visit, the date will be missing.
- Date of the last contact prior or equal to efficacy cut-off:
This date is defined as the date of the last trial contact or the efficacy cut-off date, whatever comes first.
- Date of the last trial contact:
The date of the last documented contact with the subject or a third party (including data on subject survival status).
For subjects who die after randomization the date of the last contact is set to the death date.
- Date of first double-blind dose of antithrombotic study treatment:
The date of the first dose of rivaroxaban / aspirin study medication.
- Date of last double-blind dose of antithrombotic study treatment:
The date of the last dose of rivaroxaban / aspirin study medication.

For a subject with permanent discontinuation of any study medication, the corresponding last dose date(s) will be obtained from the CRF “Study Medication Discontinuation/Restart Report”. If study medication was continued until the EOT visit, the date of the last dose of the corresponding study medication will be as reported on the EOT visit CRF.

If missing or incomplete, the date of last double-blind dose of antithrombotic study treatment is set to the latest logically possible date of antithrombotic study medication administration on or before the earliest of the subject’s following dates, the date of last trial contact, the date of death, or the efficacy cut-off date, and no earlier than the randomization date.

4.5.2 Data Scopes - amended

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

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

The ITT data scope includes all outcome events observed from randomization until the efficacy cut-off date. This will be the primary data scope for the analyses.

Analyses according to the intention-to-treat (ITT) principle will be based on the intention-to-treat analysis set (see section 5.1.1) and will include all outcome events that occur from the date of randomization and up until the efficacy cut-off date (inclusive). Subjects will be kept in the study group to which they were randomized and the follow-up period for each subject will be as long and complete as possible. This ITT data scope will be applied to the primary analysis of the primary and secondary efficacy variables and safety variables.

Data scope according to treatment (on-treatment)

The on-treatment data scope will include all outcome events observed from randomization until 2 days following permanent discontinuation of the study drug.

Analyses according to the on-treatment data scope will be based on the safety analysis set (see section 5.1.2).

This on-treatment data scope will be applied to the supportive analysis of the primary and secondary efficacy variables and safety variables.

4.5.3 Censoring rules for time-to-event variables - amended

For any time-to-event variable in this study, the following censoring rules will be applied:

Censoring rules for analyses according to the intention-to-treat principle

For analyses according to the intention-to-treat principle, randomized subjects without documentation of an event will be censored at the efficacy cut-off date or the date of the last trial contact, whatever comes first.

This censoring rule will be applied to all analyses according to the intention-to-treat principle. In the rare event that for a subject only survival status information can be retrieved at the end of the study but no information on other outcomes, the last follow-up / trial contact where survival status information was obtained will still be used to determine the censoring date for the subject and if there were no known events up to then the subject will be considered as event-free.

Censoring rules for on-treatment analyses

For on-treatment analyses, all randomized subjects with at least one dose of study medication and without documentation of an event within the on-treatment data scope will be censored at the date of last double-blind dose of antithrombotic study treatment + 2 days or the date of the last trail contact, whatever comes first.

Note that if a subject stops treatment at the EOT visit and experiences an event up to 2 days thereafter, the event will be counted in this analysis but not in the primary analysis.

4.5.4 Determination of baseline values

Baseline is defined as the last non missing value until and including the day of randomization visit.

4.5.5 Handling of repeated measurements - amended

In case of multiple measurements per post baseline visits, the 1st non-missing value per visit will be taken for analysis.

In case of multiple assessments at different (unscheduled) post baseline visits for TEE, TTE, or questionnaires, the 1st non-missing assessment will be taken for analysis, others will be listed.

4.6 Determination of sample size

The study is event-driven and it is estimated that 7000 patients (3500 per treatment group) need to be randomized in order to have approximately 450 patients experiencing a confirmed primary efficacy outcome event using the ITT data scope. This number of events will allow the demonstration of superiority of rivaroxaban compared to ASA with regard to the primary

outcome with a power of 90% and a one-sided level of significance $\alpha=0.025$ under the following assumptions:

- An average yearly event rate of the composite primary efficacy outcome of 3.8% in the ASA group (4.0% for patients with age ≥ 60 years, 2.0% for 10% of patients with age < 60 years)
- Effect size: A 30% RRR for stroke and systemic embolism in the rivaroxaban group compared to ASA
- Length of the recruitment period is 2 years and the total study duration is 3 years
- Approximately 10% of patients will permanently discontinue study medication in the first year and 7% in following years
- Approximately 5% of patients with a diagnosis of AF will switch to standard treatment during study conduct
- Approximately 3% patient deaths per year and 1% of patients lost to follow-up per year

Under these assumptions the expected RRR to be observed in this study would be 26% for the primary efficacy outcome.

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

Sample size estimation was based on a Statistical Analysis Software (SAS) macro provided by [Shih \(1995\)](#).

5. Analysis Sets

5.1 Assignment of analysis sets

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

5.1.1 Intention-to-treat analysis set (ITT)

The intention-to-treat analysis set, also termed full analysis set in the International Conference on Harmonization (ICH) E9 guideline, will include all randomized subjects.

5.1.2 Safety analysis set (SAF)

The safety analysis set will include all randomized subjects who received at least one dose of study medication.

6. Statistical Methodology

6.1 Population characteristics

6.1.1 Disposition

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

- Study sample sizes (subjects enrolled, randomized, and valid for Safety analysis set) by region and country
- Study sample sizes by country and site
- Subject disposition
- Number of subjects and primary reasons for screening failures (only overall)
- Number of subjects and primary reasons for permanent discontinuation of study medication (by treatment group and overall for SAF)
- Number of subjects and primary reasons for discontinuation of study follow-up (by treatment group and overall for ITT and SAF)
- Number of subjects withdrew consent as well as Lost to Follow-up

Kaplan-Meier plots will be used to show:

- Time from randomization to last study medication,
- Time from randomization to last contact prior or equal to efficacy cut-off,
- Time from randomization to last trial contact

by treatment group and overall for ITT and SAF.

6.1.2 Demographics

Demographic variables and baseline characteristics will be summarized by treatment group and overall in the ITT and SAF. Summary statistics will be presented for metric variables. Frequency tables will be presented for categorical variables.

Demography includes age, gender, race, ethnicity, region, body height, body weight, body mass index (BMI) and smoking history. Age, body weight and BMI will each be given as continuous variable and categorized with the following categories:

- Age: <60; 60-75; >75 years (for publication: <75; ≥75 years) additionally <60; ≥60 years
- BMI: < 25; ≥ 25 to < 30; ≥ 30kg/m² (for publication: < 30; ≥ 30kg/m²)
- Weight: <70; 70-90; >90 kg (for publication: <50; 50-100; >100 kg)

The following additional baseline characteristics will be analyzed:

- Sex: male; female
- Race: White; Black; Asian; American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; Not reported; Mixed
- Region: North America; South America; Western Europe; Eastern Europe; Asia (see Appendix B for definition)
- eGFR: <50; 50-80; >80 mL/min/1.73m²
- Stroke or TIA prior to qualifying event: yes or no
- Time from qualifying stroke to randomization: ≤30 days; 30 days to 3 months; > 3months
- Presence of patent foramen ovale: present or absent / not known
- Cardiac rhythm monitoring: <48; ≥ 48 hours
- Hypertension: yes or no
- Diabetes: yes or no
- Heart failure: yes or no
- Tobacco use: never, former, current

6.1.3 Medical history

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

6.1.4 Protocol Deviations

A summary of major protocol deviations will be given by frequency tables showing the number of subjects with major protocol deviations overall, by type of deviation. Analysis will be based on ITT.

Types of major protocol deviations include:

- Significant inclusion criteria not fulfilled
- Significant exclusion criteria fulfilled
- Failure to obtain informed consent before initiation of study procedures

- Prohibited medication use
- Failure to report SAE
- Failure to report outcome event
- Other safety

6.1.5 Prior and Concomitant Medications

Frequency tables by type of medication will be provided for prior medications prior to stroke (for antiplatelets and anticoagulants) and prior to randomization (for all) and separately for concomitant medication continued after randomization, for visits every 12 months, at EOT and post-baseline, i.e. counting every medication that was taken at least once on or after randomization. Analyses will be by treatment group and overall based on ITT.

Prior and concomitant medications from the “Concomitant Medications report CRF 350” will be analyzed according to the given categories. Other concomitant medication will be coded by Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization Drug Dictionary (WHO-DD) using the version as outlined in the Trial Summary (TS) domain and listed in section 16 of CSR.

Separately the number of patients receiving ASA at any time-point after randomization and before last dose of study drug will be displayed distinguishing ASA doses of ≤ 100 mg and > 100 mg.

6.1.6 Extent of Exposure and Compliance - amended

All analyses related to intake of study medication will be by treatment group and overall based on SAF.

The treatment duration will be calculated (date of last study medication- date of first study medication+1 day) and analysed descriptively. Additionally the number of subjects by treatment duration category will be given. Categories will include all subjects with at least 3 months, 6 months, 9 months, 12 months, 18 month, 24 month treatment duration.

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

The number of tablets taken will be calculated (tablets dispensed-tablets returned) and analysed descriptively, as well as corresponding extent of exposure (number of tablets taken*dose).

Compliance (%) = $\text{MIN}(\text{Compliance_Riva}, \text{Compliance_ASA})$

Compliance_Riva (%) = $\frac{\text{Number of Riva tablets taken} \times 100}{\text{Number of days with planned tablet intake}}$

Compliance_ASA (%) = $\frac{\text{Number of ASA tablets taken} \times 100}{\text{Number of days with planned tablet intake}}$

Number of tablets taken = 2×110 – returned tablets of pack 1 – returned tablets of pack 2 (+ tablets of unscheduled resupply – returned tablets of resupply)
(two bottles of medication for each of the medications: Riva/ASA)

Number of days with planned tablet intake = visit date – medication start date +1 (– number of days with temporary interruption)

Compliance will be tabulated as entered in the CRF and summarized for the whole study. The number of subjects with at least 80% compliance will be presented.

6.2 Efficacy

6.2.1 Primary efficacy variable

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

- Stroke (ischemic, hemorrhagic, and undefined stroke, TIA with positive neuroimaging)
- Systemic embolism

6.2.2 Secondary efficacy variables

The secondary efficacy variables of this study are the time from randomization to first occurrence of:

- Cardiovascular death (CV death; including death due to hemorrhage and death with undetermined/unknown cause), recurrent stroke, systemic embolism, and MI
- All-cause mortality
- Individual components of the primary and secondary efficacy outcomes (stroke, CV death, and MI) as well as ischemic stroke, and disabling stroke (modified Rankin score 4 and 5)

These are listed in the order of sequential testing.

6.2.3 Subgroup variables

The following subgroup analyses based on baseline demographics are planned for the comparison of the primary efficacy and safety outcomes:

- Age: <60; 60-75; >75 age (for publication: <75; ≥75 years)
additionally <60; ≥60 years
- Sex: male; female
- Race: White; Black; Asian; other

- Region: North America; South America; Western Europe; Eastern Europe; Asia
- BMI: < 25; ≥ 25 to < 30; ≥ 30kg/m² (for publication: < 30; ≥ 30kg/m²)
- Weight: <70; 70-90; >90 kg (for publication: <50; 50-100; >100 kg)
- eGFR: <50; 50-80; >80 mL/min
- Stroke or TIA prior to qualifying stroke: yes or no
- Time from qualifying stroke to randomization: ≤30 days; 30 days to 3 months; > 3months
- Presence of patent foramen ovale: present or absent / not known
- Cardiac rhythm monitoring: <48; ≥ 48 hours
(≥ 48 hours is fulfilled if in-hospital telemetry was performed and “≥48 hrs” is ticked, or ECG Holter was performed and duration is ≥ 48 hours, or other type of prolonged monitoring was performed or different types of monitoring have been used and total duration is ≥ 48 hours; ranges will be summed up using mid of the range)
- Hypertension: yes or no
- Diabetes: yes or no

Higher absolute efficacy event rates are expected for the following subgroups: older age, females, renal impairment, stroke or TIA prior to qualifying event, hypertension, and diabetes. Even though rivaroxaban has not been tested in patients with ESUS, based on earlier studies with rivaroxaban a consistent (relative) treatment effect across all of the planned subgroups is expected.

A limited number of additional subgroup analyses may be proposed by the Steering Committee.

The randomization was stratified by the dichotomic age group variable for age below 60 years (No/Yes) and by country.

6.2.4 Analysis of the primary efficacy variable

The primary analysis will include events as adjudicated by the ICAC and will be based on the ITT analysis set using the ITT data scope.

In order to evaluate whether rivaroxaban is superior to ASA in prolonging the time to a primary efficacy (PE) outcome event in patients with ESUS, the following null hypothesis (H_0) will be tested at the significance level of 0.025:

$H_{0, PE}: S_R(t) = S_A(t)$ for all time points $t \geq 0$, (i.e. “there is no difference between the rivaroxaban treatment group and the ASA control group regarding the primary efficacy outcome for all time points”)

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 and S_A denotes the survival function of the ASA group.

The following decision rule to test the null hypothesis will be applied:

According to the size of this study, it is justified to assume under $H_{0, PE}$ a sufficiently close approximation of the one-sided stratified (according to dichotomic age group) log-rank test to the normal distribution. If the z-value from the one-sided log-rank test (for the difference $S_R(t) - S_A(t)$ with stratification) is larger than the critical quantile from the normal distribution ($z_{0.975} = 1.96$), the null hypothesis will be rejected in favor of the alternative hypothesis.

Kaplan-Meier estimates of cumulative risk and Nelson-Aalen estimates of the 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.

To derive the log-rank Z test statistic and the variance V of the log-rank statistics, SAS program code corresponding to the following will be used:

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

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

Hazard ratio and corresponding two-sided 95% confidence intervals will be estimated based on an age-group stratified Cox proportional hazards models. 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. Censoring will be assumed independent of the treatment group assignment.

For the analysis of the primary outcome in this study, the hazard function $h(t)$ is the chance that an individual experiences an event of the primary efficacy outcome in the next instant in

time, given that the individual has not had such an event up to time t . For example, for the comparison of rivaroxaban with ASA (control), the corresponding stratified Cox proportional hazards model can be described by the following equation:

$$h_k(t, x_i) = h_{0k}(t) \exp(\beta x_i),$$

where

$h_k(\cdot)$ hazard function for primary efficacy outcome for stratum k , $k = 1, 2$ (k represents age group stratification factor), as a function of time and subject's covariates

$h_{0k}(\cdot)$ unspecified underlying baseline hazard function for primary efficacy outcome per stratum k ; hazard of an individual with $x_i = 0$

t time (in days) relative to the randomization date

x_i treatment group of subject i

β unknown parameter (to be estimated); hazard ratio = $\exp(\beta)$

SAS program code corresponding to the following will be used:

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

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

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

Subjects without a primary efficacy outcome event will constitute a right-censored observation (see section 4.5.3 for censoring rules). Primarily, for the time-to-event analysis the censoring mechanism will be assumed to be non-informative. Additional sensitivity analyses will be performed in order to evaluate the robustness of the statistical results under different assumptions (see section 6.2.7).

6.2.5 Analysis of secondary efficacy variables

A single primary efficacy outcome will maintain strict control of the type I error rate. If the primary efficacy outcome is statistically significant, the secondary efficacy outcomes will be tested in a sequential manner according to the order as listed in section 6.2.2.

If the superiority of rivaroxaban for the primary outcome is declared, the following alternative hypotheses, superiority of rivaroxaban compared with ASA for the secondary efficacy outcomes will be tested in the sequential order. That is, the subsequent ordered secondary outcome will be tested only if superiority can be shown for the previous outcomes.

If an individual test during any step is not statistically significant, further testing may continue but significance will not be claimed. This hierarchical testing procedure will control the global Type 1 error level.

The primary analysis of the secondary variables will include events as adjudicated by the ICAC and will be based on the ITT analysis set using the ITT data scope.

The first secondary efficacy variable (SE1) of this study is the time from randomization to first occurrence of cardiovascular death (including death due to hemorrhage), recurrent stroke, systemic embolism, or MI. The following null hypothesis will be tested at the significance level of 0.025:

$$H_{0, SE1}: S_{R1}(t) = S_{A1}(t) \text{ for all time points } t \geq 0,$$

The one-sided alternative hypothesis will be:

$$H_{1, SE1}: S_{R1}(t) > S_{A1}(t) \text{ for at least one time point } t \geq 0, \text{ and } S_{R1}(t) \geq S_{A1}(t) \text{ for all time points } t \geq 0,$$

where S_{R1} denotes the survival function of the rivaroxaban and S_{A1} denotes the survival function of the ASA group.

The second secondary efficacy variable (SE2) of this study is the time from randomization to first occurrence of death from any cause. The following null hypothesis will be tested at the significance level of 0.025:

$$H_{0, SE2}: S_{R2}(t) = S_{A2}(t) \text{ for all time points } t \geq 0,$$

The one-sided alternative hypothesis will be:

$$H_{1, SE2}: S_{R2}(t) > S_{A2}(t) \text{ for at least one time point } t \geq 0, \text{ and } S_{R2}(t) \geq S_{A2}(t) \text{ for all time points } t \geq 0,$$

where S_{R2} denotes the survival function of the rivaroxaban and S_{A2} denotes the survival function of the ASA group.

The analysis methods will be those described for the primary efficacy outcome.

The same analysis will be performed for the individual components of the primary and secondary efficacy outcomes (stroke, CV death, and MI) as well as ischemic stroke, and disabling stroke (modified Rankin score 4 and 5).

6.2.6 Subgroup analysis

Subgroup analyses for the efficacy and safety outcomes will be performed based on the same analysis sets and data scopes as in the main analyses of the study outcomes. The subgroup analyses will be presented descriptively without formal hypotheses testing. Additionally forest plots will be generated.

Homogeneity of treatment effect in subgroups, both in magnitude and direction, will be assessed by adding a covariate for the subgroup variable and the corresponding treatment-subgroup interaction to the respective (age-group stratified) Cox proportional hazards model used in the main analysis. Additionally the hazard ratio for the treatment effect will be estimated separately within each level of a subgroup variable using the same Cox proportional hazards.

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

6.2.7 Sensitivity analyses - amended

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

The analysis of the primary and secondary efficacy variables as described in section 6.2.4 and 6.2.5 will be repeated based on the safety analysis set using the on-treatment data scope.

The analysis of the primary and secondary efficacy variables as described in section 6.2.4 and 6.2.5 will be repeated counting outcome events as reported by the investigators.

The analysis of the primary and secondary efficacy variables as described in section 6.2.4 and 6.2.5 will be repeated using the Cox proportional hazard model without stratification.

The analysis of the primary and secondary efficacy variables as described in section 6.2.4 and 6.2.5 will be repeated counting adjudicated outcome events up to the last trial contact date, i.e. including also events after the efficacy cut-off date.

Despite all efforts it will be hard to completely avoid loss to follow-up within this study (White).

6.3 Pharmacokinetics / pharmacodynamics

Not applicable

6.4 Safety

6.4.1 Adverse events - amended

Adverse events (AEs) will be coded by MedDRA. The version number of MedDRA used for the analyses will be stored in the clinical database/system set-up. A listing will be provided linking the original investigator terms and the coded terms.

Analyses of reported adverse events will be performed based on the safety analysis set.

In case of uncertainty (e.g., missing or incomplete dates), adverse events will be classified as “treatment emergent” following the worst case approach.

An overall summary of SAEs and treatment-emergent (TE) AEs will be generated by treatment group and overall.

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

Serious adverse events (SAEs), AEs leading to discontinuation and AEs of particular concern will be listed. The date, relative day (to study medication) and phase of the study (pre-treatment, during treatment, post-treatment) will be included.

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

Adverse events matching the SMQ Haemorrhage terms (excl laboratory terms) will be excluded from the AE analysis to avoid double counting of events. This is affecting data from Japan where bleeding events are additionally reported as AEs. In general bleeding events are reported separately and analyzed as described in the following sections.

6.4.2 Primary safety variable

The primary safety variable is the time from randomization to time of first occurrence of a major bleeding (ISTH) defined as a bleeding event that meets at least one of the following criteria:

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), and/or
- Clinically overt bleeding associated with a recent decrease in the hemoglobin level of ≥ 2 g/dL (20 g/L; 1.24 mmol/L) compared to the most recent hemoglobin value available before the event, and/or
- Clinically overt bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood

6.4.3 Secondary safety variables

The secondary safety variables are the time from randomization to time of first occurrence of:

- Life-threatening bleeding, defined as a subset of major bleeding that meet at least one of the following criteria:
 - Fatal bleeding
 - Symptomatic intracranial bleeding
 - Reduction in hemoglobin of at least 5 g/dl (50 g/l; 3.10 mmol/L)
 - Transfusion of at least 4 units of packed red cells or whole blood
 - Associated with hypotension requiring the use of intravenous inotropic agents
 - Necessitated surgical intervention
- Clinically relevant non-major bleeding, defined as non-major overt bleeding but
 - Requires medical attention (e.g., hospitalization, medical treatment for bleeding), and/or
 - Is associated with a study drug interruption of more than 14 days.
- Intracranial hemorrhage

6.4.4 Other safety variables

All bleeding events will be analyzed. In addition to the analysis according to ISTH as described above, bleeding events will be analyzed according to GUSTO, TIMI and BARC definitions.

Vital signs and weight will be analyzed descriptively.

Any pregnancy occurring in a study subject during the subject's participation in this study will be listed in the patient data listing.

6.4.5 Analysis of safety variables

The primary analysis of the safety variables will be based on the ITT analysis set using the ITT data scope. Additionally the safety variables will be analyzed based on the safety analysis set using the on-treatment data scope.

The primary and secondary safety variables will be tested parallel without control of the type I error level.

In order to evaluate whether rivaroxaban is different to ASA with respect to the time to a bleeding event in patients with ESUS, the following null hypothesis will be tested at the two-sided significance level of 0.05:

$$H_{0, B}: S_{RB}(t) = S_{AB}(t) \text{ for all time points } t \geq 0,$$

The two-sided alternative hypothesis will be:

$$H_{1, B}: S_{RB}(t) \neq S_{AB}(t) \text{ for at least one time point } t \geq 0,$$

where S_{RB} denotes the survival function of the rivaroxaban and S_{AB} denotes the survival function of the ASA group.

The analysis methods will be those described for the primary efficacy outcome.

The safety variables will be analyzed by subgroup as describe for the efficacy variables.

6.5 Other procedures and variables

The analysis of other variables will be by treatment group and overall and based on ITT.

Other variables are:

- Healthcare Resource Use
 - hospitalizations (total days length of stay, intensive care unit/cardiac care unit days, ward type); emergency room visits; unscheduled outpatient physician consultations; or visits related to bleeding, surgeries, other selected procedures (inpatient and outpatient); and post-stroke care (status of care, home health or rehabilitation center or long term care). Days off-work.
- European Quality of Life-5 Dimensions (EQ-5D)

- EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Assessments will be done using both a descriptive system and the subject's self-rated health on a visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'.
The following variables are of interest:
 - EQ-5D single dimensions
 - EQ-5D Visual Analogue Scale (VAS) values
 - EQ-5D index score
- EQ-5D will be analyzed separate from section 14 of CSR.
- Montreal Cognitive Assessment (MoCA)
 - The Montreal Cognitive Assessment (MoCA) test assesses several cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. For each task correctly completed, one point is assigned. All subscores are summed up and adjusted for individuals with ≤ 12 years education to derive a total score ranging between 0 (for a totally cognitive impaired subject) and a maximum of 30 points (cognitively healthy participant).
- Standard Assessment of Global-Activities in the Elderly (SAGE)
 - The SAGE questionnaire comprises 15 items, each describing an activity for which the respondent has to indicate how much difficulty the subject has encountered in performing this activity in the past month. Regarding scoring for an item, 0 points are assigned if the participants endorse the "None/never performed" response, 1 point to the "Mild" response, 2 points to the "Moderate" response, and 3 points to the "Severe" response. One additional point will be assigned when in response to question 11, 12, and 15 the respondent declares the need for help from another person or a tool to walk, jump the stairs or to bath. The total score will range from 0, describing a very independent participant over a broad spectrum of activities, to 48, describing a very dependent subject.
- Modified Rankin Score
 - The modified Rankin Score runs from 0-6, running from perfect health without symptoms to death.

- The score will be analyzed by frequency tables and bar charts comparing baseline to EOT. Wilcoxon rank-sum test will be used to give exploratory p-values comparing treatment groups.

6.6 Net clinical Benefit

The benefit-risk of rivaroxaban vs aspirin will be evaluated based on the excess number of events between treatments for events intended to be prevented (benefits) and events that may be caused (risks). Excess number of events is defined as the difference in event rate times a hypothetical population size (eg, 10,000 patients). To have a comprehensive benefit-risk evaluation, several comparisons will be considered.

The first measure of net clinical benefit in this study is the primary efficacy outcome. Although named efficacy outcome it includes not only thrombotic events, but also hemorrhagic events (hemorrhagic stroke).

The second measure of net clinical benefit is all-cause mortality.

The third measure of net clinical benefit is the composite of stroke, MI, CV death, fatal bleeding or bleeding into a critical organ.

As an overall valid measure of net clinical benefit is hard to be defined, a variety of measures will be presented side by side to allow weighting positive effects and harms. For the efficacy these will include the thrombotic events of the primary and secondary efficacy endpoints. For the safety side these will include the hemorrhagic events of the efficacy endpoint, ISTH major bleeding, life-threatening bleeding, and intracranial hemorrhage.

Other measures may be added as they may help to assess the net clinical benefit.

7. Document history and changes in the planned statistical analysis

- Draft SAP dated 30 Sep 2014
- Second SAP draft for team review dated 10 Nov 2014
- Proposed final SAP for team review dated 14 Jan 2015
- Approval of the SAP dated 2 Mar 2015
- Amendment 1 of the SAP dated 19 May 2017
- Amendment 2 of the SAP dated 20 Dec 2017

7.1 Overview Changes to SAP – Amendment 1

Editorial, administrative, and typographical corrections were made that do not affect the overall integrated SAP. These changes are not described in this section.

The following changes are introduced in SAP Version 2.0.

Modification 1: Additional interim analysis at 50% of events

Rationale: Changes reflect those in global Clinical Study Protocol amendment 2.0 to be in line with the plan for interim analyses of the IDMC Charter as requested by the IDMC.

Section affected: 4.4 Interim Analyses and Data Monitoring

Modification 2: Subgroup definition for age added and for region and cardiac rhythm monitoring clarified

Rationale: Additional age group (<60; >=60 years) is reflecting the strata used for randomization. Region definition was added. The derivation of the length of cardiac rhythm monitoring was clarified.

Section affected:

- 6.1.2 Demographics
- 6.2.3 Subgroup variables
- Appendix B: Region definition

Modification 3: Details added/corrected for descriptive statistics

Rationale: “Index stroke” was changed to “qualifying stroke” to reflect the terminology of the CRF. Wording “last contact prior to efficacy cut-off” was clarified to “last contact prior or equal to efficacy cut-off”. The analysis of medical history and concomitant medication was adapted to the CRF design (pre-defined terms). The definition of the efficacy variable component CV death was clarified to include death with undetermined/unknown cause. The SAS code provided for carrying out the stratified log-rank test has been updated to reflect the FDA preferred implementation, with the difference being how tied event times are handled. Term corrected from “AE” to “SAE” in adverse event section. Analysis method for modified Rankin score added. And the DSS was deleted following the protocol amendment.

Section affected:

- 4.5.4 Determination of baseline values (new)
- 4.5.5 Handling of repeated measurements (new)
- 6.1.3 Medical history
- 6.1.5 Prior and Concomitant Medications
- 6.2.2 Secondary efficacy variables
- 6.2.4 Analysis of the primary efficacy variable
- 6.4.1 Adverse events
- 6.5 Other procedures and variables

Modification 4: Added third measure of net clinical benefit

Rationale: The rationale is the specification of a measure for net clinical benefit that captures the major adverse events (stroke, MI, CV death) and important safety outcomes (fatal bleeding or bleeding into a critical organ). These are all likely modified by the study treatment.

Section affected:

- 6.6 Net clinical Benefit

7.2 Overview Changes to SAP – Amendment 2

Modification 5: Exclusion of bleeding events from AE reporting

Rationale: In Japan bleeding events are additionally reported as AEs. To avoid double counting, bleeding events will be excluded from the AE analysis using the SMQ Haemorrhage terms (excl laboratory terms). Bleeding events will be analyzed separately.

Section affected:

- 6.4.1 Adverse events - amended

Modification 6: Setting the efficacy cut-off date to October 5th 2017

Rationale: On October 5th 2017 the early stopping of the study was announced after the recommendation by the IDMC. The definitions of the efficacy cut-off date, the trial close-out window and the date of last contact prior or equal to the efficacy cut-off date have been adapted. This adaptation was made in the description of the ITT data scope and the ITT censoring rules accordingly. Within the sensitivity analyses section for the primary efficacy outcome the obsolete tipping point analysis has been deleted and an analysis including efficacy outcome events up to the date of the last trial contact has been added.

Sections affected:

- 1. Introduction
- 4.5.1 Analysis Dates
- 4.5.2 Data Scopes
- 4.5.3 Censoring rules for time-to-event variables
- 6.2.7 Sensitivity analyses

Modification 7: Detailed description added for the calculation of treatment compliance.

Section affected:

- 6.1.6 Extent of Exposure and Compliance

8. References

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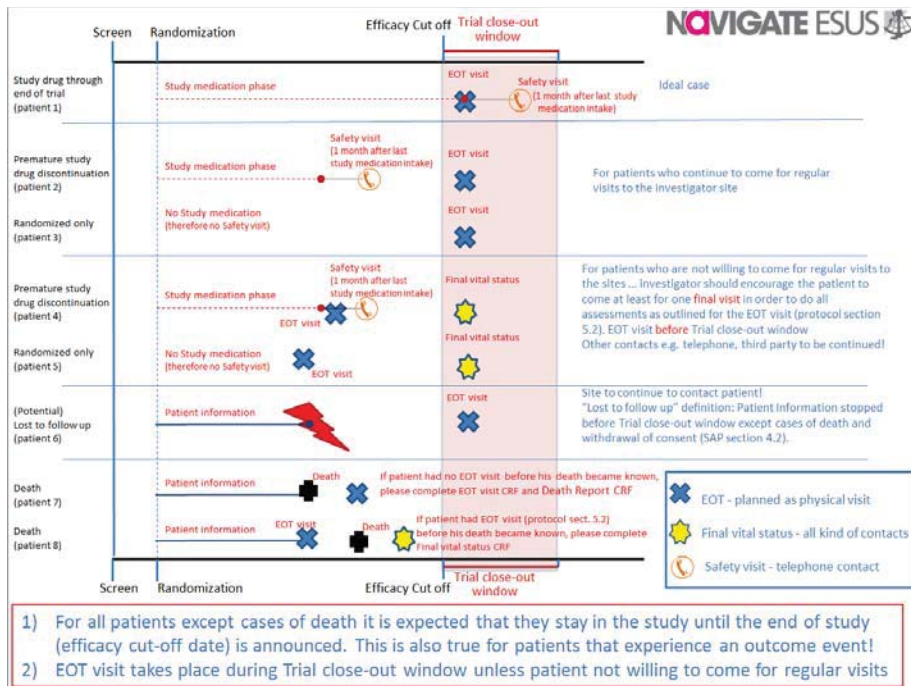
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Appendix A: Patient follow-up





Statistical Analysis Plan

Protocol No.: **BAY 59-7939/16573**

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Appendix B: Region definition - amended

For subgroup analyses according to region, countries will be assigned to regions as shown in [Table 8-1](#). below. If additional countries participate in the trial, their assignment to a region will be described in an amendment to the SAP before unblinding.

Table 8-1. Classification of countries to regions

Region	Countries
North America	Canada, USA
South America	Argentina, Brazil, Chile, Mexico
Western Europe (plus Australia, Israel, and South Afrika)	Australia, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Portugal, South Africa, Spain, Sweden, Switzerland, United Kingdom
Eastern Europe	Czech Republic, Hungary, Poland, Russian federation, Turkey
Asia Pacific	China, Japan, South Korea

Reference Number: BPD-SOP-060
Supplement Version: 6



Summary of Revisions

Extracted from page 30 and 31 of Version 2.0 of NAVIGATE ESUS
Statistical Analysis Plan (2017-06-02)

The first measure of net clinical benefit in this study is the primary efficacy outcome. Although named efficacy outcome it includes not only thrombotic events, but also hemorrhagic events (hemorrhagic stroke).

The second measure of net clinical benefit is all-cause mortality.

The third measure of net clinical benefit is the composite of stroke, MI, CV death, fatal bleeding or bleeding into a critical organ.

As an overall valid measure of net clinical benefit is hard to be defined, a variety of measures will be presented side by side to allow weighting positive effects and harms. For the efficacy these will include the thrombotic events of the primary and secondary efficacy endpoints. For the safety side these will include the hemorrhagic events of the efficacy endpoint, ISTH major bleeding, life-threatening bleeding, and intracranial hemorrhage.

Other measures may be added as they may help to assess the net clinical benefit.

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Rationale: Additional age group (<60; >=60 years) is reflecting the strata used for randomization. Region definition was added. The derivation of the length of cardiac rhythm monitoring was clarified.

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- 6.2.3 Subgroup variables
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Section affected:

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- 4.5.5 Handling of repeated measurements (new)
- 6.1.3 Medical history
- 6.1.5 Prior and Concomitant Medications
- 6.2.2 Secondary efficacy variables
- 6.2.4 Analysis of the primary efficacy variable
- 6.4.1 Adverse events
- 6.5 Other procedures and variables

Modification 4: Added third measure of net clinical benefit

Rationale: The rationale is the specification of a measure for net clinical benefit that captures the major adverse events (stroke, MI, CV death) and important safety outcomes (fatal bleeding or bleeding into a critical organ). These are all likely modified by the study treatment.

Section affected:

- 6.6 Net clinical Benefit



Summary of Revisions

Extracted from page 29 - 32 of Version 3.0 of NAVIGATE ESUS Statistical Analysis Plan (2017-12-20)

- The score will be analyzed by frequency tables and bar charts comparing baseline to EOT. Wilcoxon rank-sum test will be used to give exploratory p-values comparing treatment groups.

6.6 Net clinical Benefit

The benefit-risk of rivaroxaban vs aspirin will be evaluated based on the excess number of events between treatments for events intended to be prevented (benefits) and events that may be caused (risks). Excess number of events is defined as the difference in event rate times a hypothetical population size (eg, 10,000 patients). To have a comprehensive benefit-risk evaluation, several comparisons will be considered.

The first measure of net clinical benefit in this study is the primary efficacy outcome. Although named efficacy outcome it includes not only thrombotic events, but also hemorrhagic events (hemorrhagic stroke).

The second measure of net clinical benefit is all-cause mortality.

The third measure of net clinical benefit is the composite of stroke, MI, CV death, fatal bleeding or bleeding into a critical organ.

As an overall valid measure of net clinical benefit is hard to be defined, a variety of measures will be presented side by side to allow weighting positive effects and harms. For the efficacy these will include the thrombotic events of the primary and secondary efficacy endpoints. For the safety side these will include the hemorrhagic events of the efficacy endpoint, ISTH major bleeding, life-threatening bleeding, and intracranial hemorrhage.

Other measures may be added as they may help to assess the net clinical benefit.

7. Document history and changes in the planned statistical analysis

- Draft SAP dated 30 Sep 2014
- Second SAP draft for team review dated 10 Nov 2014
- Proposed final SAP for team review dated 14 Jan 2015
- Approval of the SAP dated 2 Mar 2015
- Amendment 1 of the SAP dated 19 May 2017
- Amendment 2 of the SAP dated 20 Dec 2017

7.1 Overview Changes to SAP – Amendment 1

Editorial, administrative, and typographical corrections were made that do not affect the overall integrated SAP. These changes are not described in this section.

The following changes are introduced in SAP Version 2.0.

Modification 1: Additional interim analysis at 50% of events

Rationale: Changes reflect those in global Clinical Study Protocol amendment 2.0 to be in line with the plan for interim analyses of the IDMC Charter as requested by the IDMC.

Section affected: 4.4 Interim Analyses and Data Monitoring

Modification 2: Subgroup definition for age added and for region and cardiac rhythm monitoring clarified

Rationale: Additional age group (<60; >=60 years) is reflecting the strata used for randomization. Region definition was added. The derivation of the length of cardiac rhythm monitoring was clarified.

Section affected:

- 6.1.2 Demographics
- 6.2.3 Subgroup variables
- Appendix B: Region definition

Modification 3: Details added/corrected for descriptive statistics

Rationale: “Index stroke” was changed to “qualifying stroke” to reflect the terminology of the CRF. Wording “last contact prior to efficacy cut-off” was clarified to “last contact prior or equal to efficacy cut-off”. The analysis of medical history and concomitant medication was adapted to the CRF design (pre-defined terms). The definition of the efficacy variable component CV death was clarified to include death with undetermined/unknown cause. The SAS code provided for carrying out the stratified log-rank test has been updated to reflect the FDA preferred implementation, with the difference being how tied event times are handled. Term corrected from “AE” to “SAE” in adverse event section. Analysis method for modified Rankin score added. And the DSS was deleted following the protocol amendment.

Section affected:

- 4.5.4 Determination of baseline values (new)
- 4.5.5 Handling of repeated measurements (new)
- 6.1.3 Medical history
- 6.1.5 Prior and Concomitant Medications
- 6.2.2 Secondary efficacy variables
- 6.2.4 Analysis of the primary efficacy variable
- 6.4.1 Adverse events
- 6.5 Other procedures and variables

Modification 4: Added third measure of net clinical benefit

Rationale: The rationale is the specification of a measure for net clinical benefit that captures the major adverse events (stroke, MI, CV death) and important safety outcomes (fatal bleeding or bleeding into a critical organ). These are all likely modified by the study treatment.

Section affected:

- 6.6 Net clinical Benefit

7.2 Overview Changes to SAP – Amendment 2

Modification 5: Exclusion of bleeding events from AE reporting

Rationale: In Japan bleeding events are additionally reported as AEs. To avoid double counting, bleeding events will be excluded from the AE analysis using the SMQ Haemorrhage terms (excl laboratory terms). Bleeding events will be analyzed separately.

Section affected:

- 6.4.1 Adverse events - amended

Modification 6: Setting the efficacy cut-off date to October 5th 2017

Rationale: On October 5th 2017 the early stopping of the study was announced after the recommendation by the IDMC. The definitions of the efficacy cut-off date, the trial close-out window and the date of last contact prior or equal to the efficacy cut-off date have been adapted. This adaptation was made in the description of the ITT data scope and the ITT censoring rules accordingly. Within the sensitivity analyses section for the primary efficacy outcome the obsolete tipping point analysis has been deleted and an analysis including efficacy outcome events up to the date of the last trial contact has been added.

Sections affected:

- 1. Introduction
- 4.5.1 Analysis Dates
- 4.5.2 Data Scopes
- 4.5.3 Censoring rules for time-to-event variables
- 6.2.7 Sensitivity analyses

Modification 7: Detailed description added for the calculation of treatment compliance.

Section affected:

- 6.1.6 Extent of Exposure and Compliance

8. References

Dubois MF, Hébert R. Imputation of missing dates of death or institutionalization for time-to-event analyses in the Canadian Study of Health and Aging. *Int Psychogeriatr*. 2001;13 Supp 1:91-7.

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