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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
Authors:	PPD		

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

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

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Abbreviations

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.

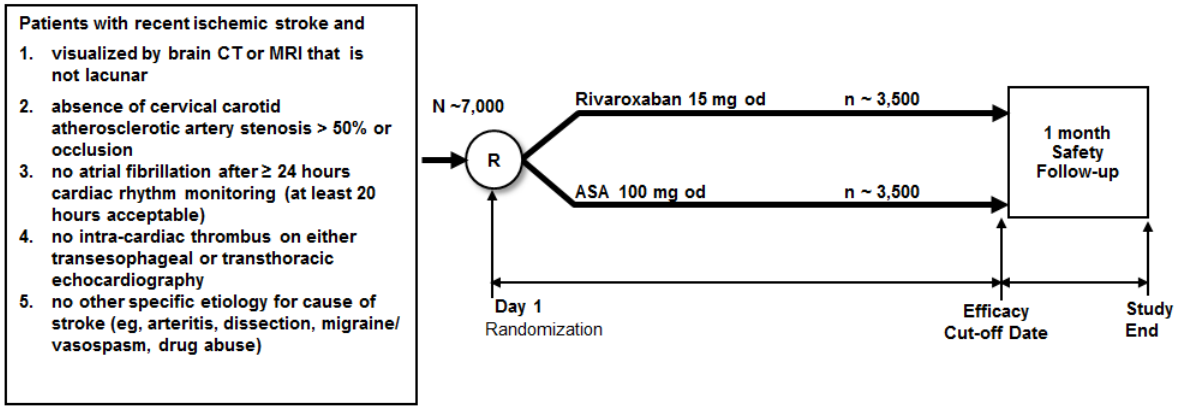
At randomization, patients will receive study medication and instructions for its administration. Thereafter, patients will return to the clinic at 1, 6, and 12 months and then every 6 months until the end of study (efficacy cut-off date) is announced. At 3 months, the patient will be contacted by telephone. 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 discontinue 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 practicioner 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 α=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.

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/m^2 (for publication: < 30; ≥ 30kg/m^2)
- 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 >100mg.

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).

$$\text{Compliance (\%)} = \text{MIN}(\text{Compliance\_Riva}, \text{Compliance\_ASA})$$

$$\text{Compliance\_Riva (\%)} = \frac{\text{Number of Riva tablets taken} \times 100}{\text{Number of days with planned tablet intake}}$$

$$\text{Compliance\_ASA (\%)} = \frac{\text{Number of ASA tablets taken} \times 100}{\text{Number of days with planned tablet intake}}$$

Number of tablets taken = 2x110 – 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/m^2 (for publication: < 30; ≥ 30kg/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 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=trtgrpn TEST=(LOGRANK);
  TIME ttevalue * ttecnsr(0);
RUN;

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

$h_k(.)$ 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

$h_{0k}(.)$ 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) = trtgrpn / RL TIES=EFRON ALPHA=0.05;
  STRATA stratumn;
RUN;

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

$H_{0,\,SE1}$: $S_{R1}(t) = S_{A1}(t)$ for all time points $t \geq 0$,

The one-sided alternative hypothesis will be:

$H_{1,\,SE1}$: $S_{R1}(t) > S_{A1}(t)$ for at least one time point $t \geq 0$, and $S_{R1}(t) \geq S_{A1}(t)$ 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:

$H_{0,\,SE2}$: $S_{R2}(t) = S_{A2}(t)$ for all time points $t \geq 0$,

The one-sided alternative hypothesis will be:

$H_{1,\,SE2}$: $S_{R2}(t) > S_{A2}(t)$ for at least one time point $t \geq 0$, and $S_{R2}(t) \geq S_{A2}(t)$ 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 rational 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

Rational: 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 adaption 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.

Shih, J. Sample size calculation for complex clinical trials with survival. Controlled Clinical Trials 1995, 16:395-407

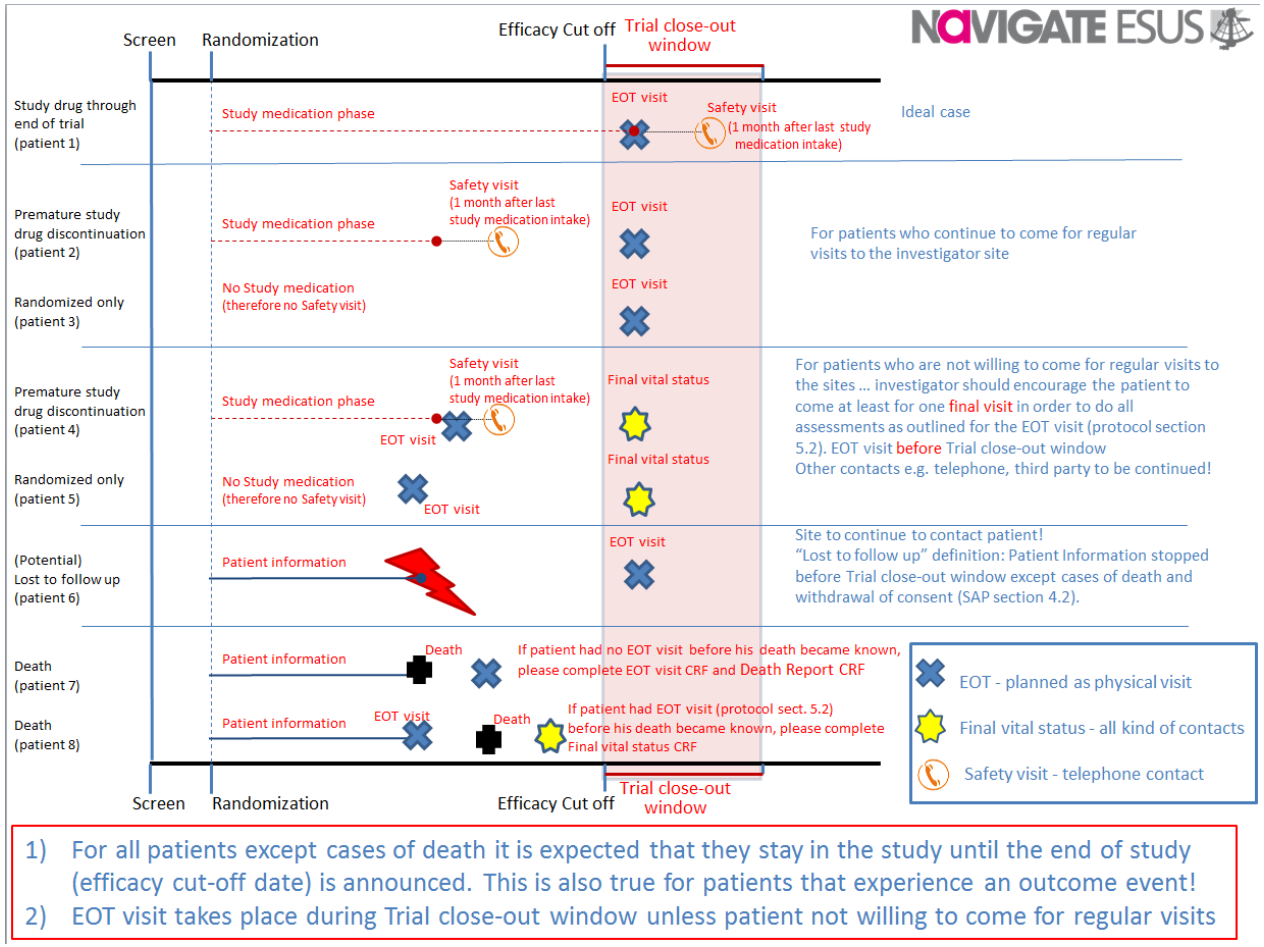
Gail M., Simon R. Testing for qualitative interactions between treatment effects and patient subsets. Biometrics 1985, 41:361-372.

Li Z., Chuang-Stein C., Hoseyni C. The probability of observing negative subgroup results when the treatment effect is positive and homogeneous across all subgroups. Drug Information Journal 2007, 41:47-56.

White, IR. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ 2011;342:d40

Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012; 367:1355-1360.

Appendix A: Patient follow-up



1) For all patients except cases of death it is expected that they stay in the study until the end of study (efficacy cut-off date) is announced. This is also true for patients that experience an outcome event!
2) EOT visit takes place during Trial close-out window unless patient not willing to come for regular visits

Appendix B: Region definition - amended

For subgroup analyses according to region, countries will be assigned to regions as shown in Table 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 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