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**Global multicenter, open-label, randomized, event-driven, active controlled study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR) to optimize clinical outcomes. (GALILEO)**

**[Global study comparing a rivAroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic vaLve rEplacement to Optimize clinical outcomes.]**

**Bayer study drug** BAY 59-7939 / JNJ-39039039 / Rivaroxaban

**[Study purpose:]** Exploratory study in a specific population after TAVR

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## Abbreviations

AE	Adverse event	IC	Informed consent
AF	Atrial fibrillation	INR	International normalized ratio
AS	Aortic stenosis	ISTH	International Society on Thrombosis and Haemostasis
ASA	Acetylsalicylic acid	ITT	Intention-to-treat
ATC	Anatomical Therapeutic Chemical (ATC) Classification System	IxRS	Interactive Web or Voice Response System
BARC	Bleeding academic research consortium	ln	Natural Logarithm
CAD	Coronary artery disease	mg	Miligram
CEC	Clinical Event Committee	MI	Myocardial infarction
CI	Confidence interval	min	Minutes
CNS	Central nervous system	ML	Maximum partial likelihood method
COPD	Chronic Obstructive Pulmonary Disease	N/A	Not applicable
CRF	Case report form	NI	Non-inferiority
CSP	Clinical study protocol	NOAC	Non-vitamin K oral anticoagulants
DAPT	Dual-antiplatelet therapy	NOAF	New-onset atrial fibrillation
DSMB	Data safety monitoring board	od	Once-daily
DTE	Death or first adjudicated thromboembolic event	OT	On-treatment
DVT	Deep vein thrombosis	PBE	Primary bleeding event
e.g.	Exempli gratia (for example)	PE	Pulmonary embolism
eCRF	Electronic case report form	SAP	Statistical analysis plan
eGFR	Estimated glomerular filtration rate	TAVR	Transcatheter aortic valve replacement
EOT	End-of-treatment	TEE	Transesophageal echocardiogram
et al.	Et alii (and others)	TIA	Transient ischemic attack
etc.	Et cetera (and so on)	TIMI	Thrombolysis in Myocardial Infarction
FAS	Full analysis set	TTE	Transthoracic echocardiogram
H <sub>0</sub>	Null Hypothesis	US(A)	United States (of America)
H <sub>1</sub>	Alternative Hypothesis	VARC	Valve academic research consortium
HR	Hazard ratio	VKA	Vitamin K antagonists
i.e.	Id est (that is)	VRM	Validity Review Meeting

## 1. Introduction

Calcific aortic valve stenosis (AS) is characterized by an increased thrombogenic and inflammatory profile<sup>1</sup>. Long-term oral antithrombotic treatment after transcatheter aortic valve replacement (TAVR) aims to prevent complications, notably ischemic stroke and myocardial infarction (MI) as well as thromboembolism related to deep vein thrombosis, pulmonary embolism, valve thrombosis, or systemic embolism while minimizing bleeding risk. The baseline risk for ischemic and thromboembolic complications is determined by comorbidities such as concomitant coronary artery disease (CAD), which is present in 20–70% of patients eligible for TAVR. Furthermore, in-hospital atrial fibrillation (AF) may occur in about one-third of patients referred for TAVR<sup>2</sup>.

Therefore, dual-antiplatelet therapy (DAPT) is not optimal in targeting the underlying pathophysiological mechanisms in the actual standard of care after TAVR due to severe AS. Rivaroxaban, through the inhibition of the pathways underlying the increased thrombogenicity, may effectively prevent thrombotic complications after TAVR without exposing this elderly<sup>3</sup> population to an increased bleeding risk.

Stroke and transient ischemic attack (TIA) are estimated to occur in 5% of patients at 30 days and 10% of patients at 1 year after TAVR, based on the PARTNER cohorts, on the CoreValve trial, and on a large meta-analysis by Athappan et al<sup>4, 5, 6</sup>. Approximately half of the strokes within 30 days post TAVR occur within the first 24 hours<sup>7</sup>.

The investigation of anticoagulation in the medical management of patients following TAVR is further justified by the fact that the incidence of new-onset atrial fibrillation (NOAF) after TAVR may be underestimated. Dumont and his group reported that one-third of patients with no prior history of AF had NOAF after TAVR and this was associated with a higher rate of stroke/systemic embolism at 30 days and 1 year<sup>2</sup>. Thus, despite the number of mechanisms that may be involved in stroke after TAVR, there is a particularly strong relationship between post procedural AF and stroke occurring after 24 hours suggesting that cardioembolic origin might significantly contribute to stroke after TAVR. Finally, the clustering of thromboembolic risk factors in TAVR populations such as renal impairment (close to 80%), severe chronic obstructive pulmonary disease (COPD) (15%), coronary artery disease (70%), peripheral vascular disease (30%), and moderate to severe mitral regurgitation (30%), could indicate that long-term anticoagulation therapy (beyond 12 months) after TAVR can be of value.

For further information see the Clinical Study protocol 2015-001975-30 version 3.0 dated 17 August 2016 where upon this SAP is based.

## 2. Study Objectives

### 2.1 Primary Objective(s)

The aim of this study is to assess whether a rivaroxaban-based anticoagulation strategy, following successful TAVR, compared to an antiplatelet-based strategy, is superior in reducing death or first thromboembolic events (DTE). This comparison is preceded by a non-inferiority test that must be satisfied.

A second aim of this study is to assess the primary bleeding events (PBE) of the rivaroxaban-based strategy, following TAVR, compared to an antiplatelet-based strategy. PBE is defined as the composite of life-threatening, disabling, or major bleeding events and is classified according to the VARC definitions following the BARC classification.

### 2.2 Secondary Objectives

The secondary efficacy objectives are to compare the effects of the rivaroxaban-based strategy and antiplatelet-based strategy with respect to the net-clinical-benefit, defined as the composite of death or first thromboembolic events and life-threatening, disabling, or major bleeding events classified according to the VARC definitions following the BARC classification.

Whereas the secondary safety objectives are safety criteria with respect to bleeding (Thrombolysis in myocardial infarction [TIMI] major or minor bleeds, International society on thrombosis and haemostasis [ISTH] major bleeding, and BARC 2, 3, or 5 bleeds).

### 2.3 Other Objectives

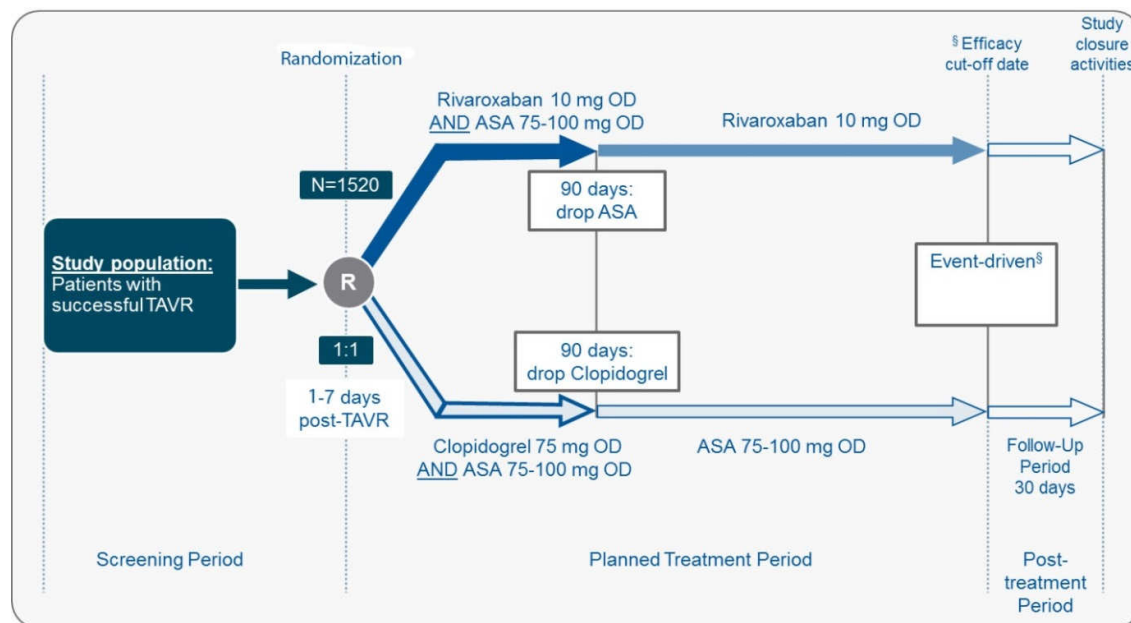
Other secondary efficacy and safety objectives are to compare the effects of a rivaroxaban based strategy and an antiplatelet-based strategy with respect to the individual components of the composite of DTE and of the composite of life threatening, disabling, or major bleeding, respectively.

The effect of rivaroxaban-based strategy, following successful TAVR, compared to an antiplatelet-based strategy, on the mean transaortic valve pressure gradient at 360 days as measured by echocardiography will be assessed as an exploratory study endpoint.

### 3. Study Design

### 3.1 Study flow diagram

The study design is detailed in Figure 1 and in section 3.2



**Figure 1: Study flow diagram.**

### Successful transcatheter aortic valve replacement (TAVR)

§ The duration of the planned treatment period will depend on the time needed to reach the efficacy cut-off date, i.e. to collect the predefined number of efficacy endpoints or earlier if the event rate is unexpectedly low. The expected duration of the treatment is 720 days but may be adjusted depending upon the rate of subject recruitment and efficacy event rates.

R, randomization; ASA, acetylsalicylic acid; OD, once-daily.

### 3.2 Study plan

This is an event-driven, randomized, open-label with blinded endpoint evaluation, parallel-group, active-controlled, and multicenter study comparing the efficacy and safety of a rivaroxaban-based strategy versus a standard antiplatelet-based strategy for the prevention of ischemic and thromboembolic complications while minimizing the bleeding risk in subjects who successfully underwent TAVR.

The study is divided into a screening period, a planned treatment period, and an observational post-treatment period.

The screening period begins after TAVR. Subjects who have successfully undergone a TAVR procedure of an aortic valve stenosis (either native or valve-in-valve) are included. All inclusion and exclusion criteria should be reviewed before IC is signed. Subjects with an



ongoing/continued indication for oral anticoagulation at the time of randomization are excluded from this study.

Once IC has been obtained and eligibility has been confirmed, subjects are randomized (1:1), to a rivaroxaban-based strategy or to an antiplatelet-based strategy. Randomization must take place within 1-7 days post-TAVR and before hospital discharge. Stratification by site is performed to ensure balance across potential local differences in treatment practices.

The assigned treatment strategy is implemented after randomization.

In each strategy, one antiplatelet therapy agent is dropped after 90 days. This means that in the rivaroxaban-based strategy, ASA is discontinued after 90 days and rivaroxaban 10 mg is to be continued alone. Whereas, in the antiplatelet-based strategy, clopidogrel must be discontinued after 90 days and ASA is to be continued alone.

Study treatments are continued until the efficacy cut-off date, i.e. when 440 subjects are anticipated to have experienced a positively adjudicated primary efficacy endpoint, when subjects will be transitioned from the assigned strategy to an appropriate therapy, as per the clinical site standard of care. This is anticipated to occur approximately 720 days after the first patient is randomized, but may vary depending on the recruitment rate as well as the on the primary efficacy event rate. One on-site visit will be scheduled for each patient when the efficacy cut-off date is anticipated.

In the event of NOAF, study treatments are changed as follows:

Subjects randomized to rivaroxaban-based strategy: Subjects randomized to the rivaroxaban-based strategy should be switched to rivaroxaban 20 mg once-daily (or 15 mg once-daily dose for moderate renal impairment with  $eGFR < 50$  and  $\geq 30$  mL/min/1.73m<sup>2</sup>).

Subjects randomized to antiplatelet-based strategy: Subjects randomized to the antiplatelet-based strategy are switched to treatment with VKA with a target INR 2-3.

In case NOAF is diagnosed within the first 90 days after randomization, ASA 75-100 mg once-daily will be continued in both treatment arms in addition to oral anticoagulation with rivaroxaban 20 mg/ 15 mg once-daily or VKA, respectively. ASA 75-100 mg once-daily will be discontinued at 90 days after randomization and anticoagulation continued alone with rivaroxaban 20 mg/ 15 mg once-daily or VKA, respectively. NOAF subjects remain in the study, the timing of on-site visits and/or phone assessments will be kept unchanged until the efficacy cut-off date when an on-site visit and remaining study closure activities take place.

Subject contacts are planned to take place at least at 30, 90, and 180 days after randomization and from 180 days onward, every 180 days until the efficacy cut-off date is anticipated, and the study medication is stopped. Thirty days after the permanent discontinuation of the assigned study medication, a telephone assessment will be performed.

All randomized subjects should be followed until the efficacy cut-off date.

## 4. General Statistical Considerations

### 4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.3 or higher (SAS Institute Inc., Cary, NC, USA).

All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, maximum, median and quartiles will be calculated for metric data. Frequency tables will be generated for categorical data.

Tabulation of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. Percentages will be rounded to one decimal place.

In general, these summaries will be calculated separately for each treatment group but jointly for all study centers.

If not stated otherwise, all efficacy and safety analyses will be based on findings as confirmed by the Clinical Event Committee (CEC).

Events occurring on the day of randomization will be considered post-randomization, since the CEC is guided to not confirm events pre-randomization.

The validity of subjects for allocation to various populations and data scopes (FAS, pre-NOAF, post-NOAF and on-treatment) will be assessed during one or more interim and a final Validity Review Meetings (VRM) and decisions will be documented in the Validity Review Report. This SAP might be updated based on the results of the validity review meeting.

All subjects randomized will analyzed as randomized.

### 4.2 Handling of Dropouts

A subject who withdraws IC before randomization or who develops a violation of the selection criteria before randomization is defined as a screening failure. No follow-up of screening failures is performed. These screening failures will be excluded from the analyses. Only the number of screening failures and the reason for failure will be presented.

Subjects discontinuing study participation prematurely after the subject has been randomized will not be excluded from the analyses.

### 4.3 Handling of Missing Data

No imputation of data will be performed, with the following exceptions:

Missing or incomplete AE or efficacy/safety event dates will be imputed according to:

- If only the day is missing the date will be set to first day of the recorded month

- If the day and the month are missing the date will be set to the first of January of the recorded year
- If the imputed date is prior to the date of the randomization the date will be set equal to the date of the randomization

Medication dates used for the Data Scopes (see paragraph 5.2) will not be missing or incomplete, since the Study Drug Exposure form in the eCRF does not allow missing or incomplete start and stop dates.

All other missing or incomplete dates will not be imputed.

All missing or incomplete data will be presented in the subject data listing as they are recorded in the eCRF.

#### 4.4 Interim Analyses and Data Monitoring

No formal interim analysis is planned.

The Data Safety Monitoring Board (DSMB) will assess the benefit and harm given the observed rates of efficacy and safety endpoints at that time. Detailed information on the roles and responsibilities of the DSMB are described in the DSMB charter.

#### 4.5 Data Rules

For event data, the number of days from randomization will be used. For each subject, each assessment (event) will be assigned a study day with respect to the trial reference start date, which is the date of randomization of the subject.

If assessment date is on or after the trial reference start date:

Study Day = Assessment day – trial reference start date +1.

If assessment date before the trial reference start date :

Study Day = Assessment date – trial reference start date.

So Study Day 1 will indicate the event occurred at the same day the randomization was performed, Study Day 2 will indicate the event occurred the day following the day of the randomization and Study Day -1 indicates the day before randomization.

#### 4.6 Validity Review

The results of the validity review meeting will be documented in the validity review report and may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the validity review meeting will be documented in an amendment and, if applicable, in a supplement to this SAP.

## 5. Analysis Sets

### 5.1 Assignment of analysis sets

#### Full analysis set (FAS)

This subject set includes all randomized subjects, whether treated or not.

### 5.2 Data scopes

#### 5.2.1 Data scopes according to intention-to-treat principle (ITT analysis)

##### Efficacy cut-off date

When the anticipated efficacy cut-off date is set, the sponsor informs each investigational site and all subjects must return to the clinic within 6 weeks in order to have a final assessment. This assessment will coincide with the EOT visit for the subjects under treatment. The efficacy cut-off date is the date when the study treatments are discontinued. This date will be determined by the Executive Committee (see protocol 5.3.3). From this day onwards subjects will be transitioned from the assigned strategy to an appropriate therapy, as per the clinical site standard of care.

##### Censoring of follow-up in ITT analysis

Censoring of follow-up for patients is on the efficacy cut-off date, or date of last known clinical status collected from Last Clinical Status form, or date of death (by CEC adjudication) whichever comes first.

#### 5.2.2 Data scope according to on-treatment (OT analysis)

##### Date of permanent discontinuation of the randomized treatment strategy

Date of permanent discontinuation of the randomized treatment strategy is defined as follows:

##### For subjects randomized to rivaroxaban-based strategy:

- two days after last known ingestion of study rivaroxaban. This date is derived from study drug exposure form, as are the other medication start/stop dates in this section.

##### For subjects randomized to antiplatelet-based strategy:

- two days after last known ingestion of clopidogrel, ASA, or VKA (after NOAF only), whichever comes last.

##### Censoring of follow-up for subjects in OT analysis

Censoring of follow-up for patients is the efficacy cut-off date, the date of last known clinical status or date of permanent discontinuation of the randomized treatment strategy + 2 days, whichever comes first.

### 5.2.3 Data scope pre-NOAF analysis

#### **Date of NOAF requiring treatment with high dose oral anticoagulation**

Date NOAF is defined as the date where treatment with high dose oral anticoagulation for NOAF is started. Information is derived from study drug exposure form for Rivaroxaban or VKA in combination with ECG evidence of NOAF.

#### **Censoring of follow-up in pre-NOAF analysis**

Censoring of follow-up for subjects is on the efficacy cut-off date, date of last known visit or NOAF date, whichever comes first.

### 5.2.4 Data scope post-NOAF analysis

#### **Date of NOAF requiring treatment with high dose oral anticoagulation**

Date NOAF is defined as the date where treatment with high dose oral anticoagulation for NOAF is started. Information is derived from study drug exposure form for Rivaroxaban or VKA in combination with ECG evidence of NOAF.

#### **Start of follow-up in post-NOAF analysis**

Day 1 in post NOAF analysis is the date of NOAF as defined above.

#### **Censoring of follow-up in post-NOAF analysis**

Censoring of follow-up for subjects is on the efficacy cut-off date, or date of last known visit, whichever comes first.

Only subjects that start OAC treatment as described in the protocol section 7.1.1.1 and 7.1.2.1 are included from the post-NOAF analysis.

## 6. Statistical Methodology

### 6.1 Population characteristics

#### 6.1.1 Disposition

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

- Study sample size (FAS)
- Study sample size by region, country and site (FAS)

Region is defined as follows:

North America: Canada, USA

Eastern Europe: Czech Republic, Poland

Western Europe: Austria, Belgium, Denmark, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, UK

- Number of subjects by primary reason for screening failure (overall only, subjects screened)
- Number of subjects with permanent discontinuation of randomized treatment strategy (FAS)
- Number of subjects and primary reason for discontinuation from the study (FAS)

#### 6.1.2 Demographics

The following demographic and baseline characteristics will be summarized by treatment group in FAS. Summary statistics will be presented for metric variables and frequency tables will be presented for categorical variables.

- Sex (% male)
- Age (continuous, year)
- Age (categorical <median, ≥median, ≤75 year, >75 year, ≤85 year, >85 year)
- Weight (continuous, kg)
- BMI (continuous, kg/m<sup>2</sup>)
- Ethnicity (categorical as specified in eCRF)
- Race (categorical as specified in eCRF)
- Current/recent smoker (<1 year) (% yes)
- Diabetes mellitus (% yes, )
- eGFR at screening (<30 ml/min/1.73m<sup>2</sup>, ≥30 to ≤50 ml/min/1.73m<sup>2</sup>, >50 to ≤80 ml/min/1.73m<sup>2</sup>, >80 ml/min/1.73m<sup>2</sup>)

Other baseline characteristics may be added.

### 6.1.3 Medical history

Medical history data will be evaluated by treatment group in FAS. Frequency tables, showing the number of subjects with medical history findings that started before signing of the informed consent and that are considered relevant to the study.

Medical history findings, of the pre-specified CRF items as listed, 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 FAS. Medical History of the category “Other” will be presented if the frequency of PT is 5% or higher. In addition, medical history will be presented by the pre-specified terms as listed in the CRF:

- Arterial hypertension (% yes)
- Congestive heart failure (left ventricular dysfunction) (% yes)
- Myocardial infarction (% yes)
- Percutaneous Coronary Intervention (% yes)
- Coronary Artery Bypass Graft (% yes)
- Stroke (% yes)
- Transient Ischemic Attack (% yes)
- Peripheral artery disease (% yes)
- Non-CNS systemic embolism (% yes)
- Venous thromboembolism (% yes)
- COPD (% yes)

### 6.1.4 TAVR details

The following TAVR details will be summarized by treatment group in FAS. Summary statistics will be presented for metric variables and frequency tables will be presented for categorical variables as specified in [4.1](#)

- TAVR due to subjects frailty (% yes)
- EuroScore II (final) (continuous)
- STS score (final) (continuous)
- Brand name of aortic valve (categorical as specified in eCRF)
- Size of aortic valve (continuous)
- Valve in valve procedure (% yes)

### 6.1.5 Randomization timing

Timing of randomization (number of days post TAVR) is summarized by treatment group in FAS.

### 6.1.6 Protocol deviations

Protocol deviations will be summarized by treatment group in FAS. Frequency tables will be presented by type of deviation.

### 6.1.7 Prior and concomitant medications

Frequency tables by ATC code will be provided for prior medications prior to randomization and for concomitant medication post-randomization. The summaries will be by treatment group and overall based on FAS.

### 6.1.8 Extent of exposure and Compliance

All summaries related to intake of study medication will be by treatment group based on FAS.

The treatment duration (date of last study medication – date of start first study medication +1) will be summarized descriptively.

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

## 6.2 Efficacy

The primary efficacy endpoint is death or first adjudicated thromboembolic event (DTE), defined as the adjudicated composite of

- All-cause death
- Any stroke
- Myocardial infarction (MI)
- Symptomatic valve thrombosis
- Pulmonary embolism (PE)
- Deep vein thrombosis (DVT)
- Non-central nervous system (CNS) systemic embolism

The endpoint definitions are located in sections 16.1 and 16.2 of the protocol.

The secondary efficacy endpoints, analyzed hierarchically, are



- The adjudicated composite of cardiovascular death (including unknown of unexplained death), any stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis, or non-CNS systemic embolism
- The net-clinical-benefit defined as the adjudicated composite of all-cause death, any stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis, non-CNS systemic embolism (efficacy); life-threatening, disabling and major bleeds (safety).

### 6.2.1 Analysis of the efficacy endpoints

The analysis of the primary efficacy endpoint (DTE) and the secondary efficacy endpoints are performed on the FAS under the ITT scope. See chapter 5 for details.

In order to preserve the type I error rate for efficacy testing, there is a hierarchy in testing for the efficacy endpoints, first a non-inferiority testing of the primary efficacy endpoint (DTE) is performed. If non-inferiority can be claimed for the rivaroxaban-based strategy a superiority testing of the primary efficacy endpoint (DTE) is performed. If superiority can be declared for the rivaroxaban-based strategy the secondary efficacy and net-benefit variables are tested sequentially in a hierarchical order, first the composite of cardiovascular death, any stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis, or non-CNS systemic embolism, second the net-clinical-benefit defined as the adjudicated composite of all-cause death, any stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis, non-CNS systemic embolism (efficacy); life-threatening, disabling and major bleeds (safety). These are tested at a one-sided significance level of 2.5%

If there is strong evidence of non-proportionality, the estimation of time-dependent hazard ratios will be considered.

The analysis of the primary efficacy endpoint is visualized in [flowchart 1](#) in appendix I, the analysis of the secondary efficacy endpoints are visualized in [flowchart 2](#) in appendix I.

Details of the tests in the following sections.

#### 6.2.1.1 Testing for non-inferiority

Testing for superiority of the rivaroxaban-based strategy for the primary efficacy outcome is preceded by testing for non-inferiority, in the OT data scope, tested with the non-inferiority log rank test<sup>8</sup>.

Using an non-inferiority log rank test the following (inferiority) null hypothesis ( $H_0$ ) is tested at a one-sided significance level of 2.5%:

$H_0: \widehat{HR}(t) \geq 1.20$  for all time points  $t \geq 0$ , (i.e. “the hazard for the primary efficacy endpoint in the rivaroxaban-based treatment group is more than 20% larger than that in the antiplatelet-based control group regarding”)

The one-sided alternative hypothesis ( $H_1$ ) is:

$H_1: \widehat{HR}(t) < 1.20$  for all time points  $t \geq 0$ , (i.e. “the hazard in the rivaroxaban-based treatment group for the primary efficacy endpoint is such that the  $\widehat{HR}$  is below 1.20”)

The following decision rule to test the null hypothesis of inferiority is applied:

With the estimated drift parameter  $\hat{q} = Z/V$  where  $Z$  is the LR statistic with its Variance  $V$  (note that  $V \approx \text{events}/4$ ) and  $\widehat{HR} = \exp(-\hat{q})$ , the upper 97.5% limit of the confidence interval for  $\widehat{HR}$  is calculated as

$UL_{0.975}(\widehat{HR}) = \exp\left(-\left(\hat{q} - \frac{1.96}{\sqrt{V}}\right)\right)$  and will be compared with the NIM of 1.2. The null hypothesis  $H_0: HR \geq 1.2$  will be rejected if  $UL_{0.975}(\widehat{HR}) < 1.2$

If the null-hypothesis of inferiority ( $H_0$ ) is rejected and non-inferiority of the rivaroxaban-based strategy (relative to the antiplatelet-based strategy) with regard to the primary efficacy endpoint can be claimed, proceed to section [6.2.1.2](#).

The following SAS code can be used to obtain the LR statistic:

```
ods output LogRankHomCov=work.LRHC HomStats=work.HomStats ;
proc lifetest data=work.infile alpha=0.025 method=km notable ;
time d2fDTE * DTE(0) ;
strata treat /test=(logrank) ;
run;

*from ODS datasets to needed variables, and calculations;
data work.logrank (drop=treat);
merge work.lrhc (where=(treat='0') keep=treat _0 rename=(_0=V))
      work.homstats (where=(treat='0') rename=(LogRank=Z) keep=LogRank
      treat);

q=Z/V;
HR=exp(-q);
UL=exp(-(q-(1.96/sqrt(V))));
label
    Z="LR statistic"
    V="Variance of LR statistic"
    q="q"
    HR="HR"
    UL="Upper limit 0.975"
;
%put "on purpose no by statement for merge, 1 record per input dataset";
run;
/*
where
work.infile = name of source dataset
treat       = randomization code
DTE         = death and thromboembolic event
d2fDTE      = days to first DTE (since randomization)
*/
```

### 6.2.1.2 Testing for superiority

If, for the primary efficacy endpoint (DTE), non-inferiority of the rivaroxaban-based strategy can be claimed, superiority of the rivaroxaban-based strategy for the primary efficacy endpoint (DTE) is tested with the following hypothesis ( $H_0$ ) at the significance level of 2.5%

$H_0$ :  $S_{RIV}(t) = S_{APT}(t)$  for all time points  $t \geq 0$ , (i.e. “there is no difference between the rivaroxaban-based treatment group and the antiplatelet-based control group regarding the primary efficacy endpoint at all time points”)

The one-sided alternative hypothesis ( $H_1$ ) is:

$H_1$ :  $S_{RIV}(t) > S_{APT}(t)$  for at least one time point  $t \geq 0$ , and  $S_{RIV}(t) \geq S_{APT}(t)$  for all time points  $t \geq 0$  (i.e. “there is difference between the two groups in favor of the rivaroxaban-based treatment group for the primary efficacy endpoint at all time points”)

where  $S_{RIV}$  denotes the event-free survival function of the rivaroxaban-based treatment group and  $S_{APT}$  denotes the event-free survival function of the antiplatelet-based treatment group.

The following decision rule to test the null hypothesis is applied:

According to the size of this study, it is justified to assume under  $H_0$  a sufficiently close approximation of the one-sided log-rank test to the normal distribution. If the  $z$  value from the one-sided log-rank test (for the difference  $S_{RIV}(t) - S_{APT}(t)$ ) is larger than the critical quantile from the normal distribution ( $z_{0.975} = 1.96$ ), the null hypothesis is rejected in favor of the alternative hypothesis.

Kaplan-Meier curves, one-sided log rank p-value, number of patients with event and incidence rate are provided to evaluate the timing of event occurrence in the different treatment groups and the consistency of the respective treatment effects for all time points.

The following SAS code may be used:

```
proc lifetest data=work.infile notable;
  time d2fDTE*DTE(0);
  strata treat /test=(logrank);
run;
/*
where
work.infile = name of source dataset
treat       = randomization code
DTE         = death and thromboembolic event
d2fDTE      = days to first DTE (since randomization)
*/
```

If, for the primary efficacy endpoint (DTE), non-inferiority of the rivaroxaban-based strategy can be claimed and the assumption of proportional hazards is plausible (see section 6.2.1.3), Hazard ratio and corresponding two-sided 95% confidence intervals are estimated. This is based on a Cox proportional hazards model, and will be reported descriptively. The parameter estimate  $\beta$  ( $=\ln(HR)$ ), its standard error, p-value, and 95% Confidence Limits are calculated according to the maximum partial likelihood method (ML), with Breslow’s approximation for ties (phreg).

The following SAS code may be used:

```
proc phreg data=work.infile ;
    model d2fDTE*DTE(0)=treat /risklimits ;
run;
/*
where
work.infile = name of source dataset
treat       = randomization code
DTE         = death and thromboembolitic event
d2fDTE      = days to first DTE (since randomization)
*/
```

If superiority of DTE can be declared for the rivaroxaban-based strategy the secondary efficacy and net-benefit variables are tested for superiority sequentially in a hierarchical order, first the composite of cardiovascular death, any stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis, or non-CNS systemic embolism, second the net-clinical-benefit defined as the adjudicated composite of all-cause death, any stroke, myocardial infarction, symptomatic valve thrombosis, pulmonary embolism, deep vein thrombosis, non-CNS systemic embolism (efficacy); life-threatening, disabling and major bleeds (safety).

The superiority analysis are carried out under the ITT data scope.

### 6.2.1.3 Assessment plausibility of the proportional hazards assumption

If the hypothesis of non-inferiority is accepted the plausibility of the proportional hazards assumption will be assessed by visually comparing the plot of the log of cumulative hazard , in the ITT data scope, between treatments. The following SAS code may be used:

```
proc phreg data=work.infile (where=(treat=1));
model d2fDTE*DTE(0)=treat;
baseline out=work.ch_t1 cumhaz=ch;
run;
proc phreg data=work.infile (where=(treat=0));
model d2fDTE*DTE(0)=treat;
baseline out=work.ch_t0 cumhaz=ch;
run;
data work.log_ch;
set work.ch_t1
    work.ch_t0;
if ch ne 0 then log_ch=log(ch);
run;

proc sgrender data=work.log_ch template=comp_log_CH;
dynamic xvar="d2fDTE" yvar="log_ch" groupvar="treat";
run;

/*
where
```

```
work.infile = name of source dataset
treat       = randomization code
DTE         = death and thromboembolic event
d2fDTE      = days to first DTE (since randomization)
comp_log_ch = proc template for a log of cumulative hazards plot
*/
```

By additionally adding a time-varying covariate, an interaction between the predictor and the time the plausibility of proportional hazards is assessed, the following SAS code may be used:

```
proc phreg data= work.infile;
model d2fDTE * DTE (0)=treat treat_time;
treat_time = treat*log(d2fDTE);
proportionality_test: test treat_time;

run;

/*
where
work.infile = name of source dataset
treat       = randomization code
DTE         = death and thromboembolic event
d2fDTE      = days to first DTE (since randomization)
*/
```

### 6.3 Pharmacokinetics / pharmacodynamics

Not applicable.

### 6.4 Safety

#### The primary safety endpoint

The primary safety endpoint is primary bleeding event (PBE), defined as the composite of life-threatening, disabling or major bleeds classified according to the VARC definitions following the BARC classification. This is: Life-threatening or disabling bleeds; BARC type 3b, 3c or 5 and for Major bleeds; BARC type 3a.

#### The secondary safety endpoints

The secondary safety endpoints are bleeding complications according to:

- The composite of TIMI major or minor bleeds
- ISTH major bleeding
- The composite of BARC 2, 3 or 5 bleeds

#### Investigator reported events

- Serious adverse events (SAEs)

- Adverse events of special interest
  - Pericardial bleedings
  - Pulmonary alveolar bleedings/pulmonary bleeding
- Non-serious Adverse Events

#### 6.4.1 Analysis of the safety endpoints

##### 6.4.1.1 Analysis of the primary safety endpoint

The descriptive analysis of the primary safety endpoint (PBE) and the secondary safety endpoints are performed on the FAS under the ITT scope

Kaplan-Meier curves, one-sided log rank p-value, number of patients with event and incidence rate are 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.. This is done analogue to the primary efficacy endpoint as described in section [6.2.1.2](#)

If the assumption of proportional hazards is plausible (see section [6.2.1.3](#)), Hazard ratio and corresponding two-sided 95% confidence intervals are estimated.. This is done analogue to the primary efficacy endpoint as described in section [6.2.1.2](#).

The analysis of the primary safety endpoint is visualized in [flowchart 3](#) in appendix I.

##### 6.4.1.2 Analysis of the secondary safety endpoints

The secondary safety endpoints are descriptively analyzed similar to those for secondary efficacy variables, without any sequential order.

The analysis of the secondary safety endpoints are visualized in [flowchart 2](#) in appendix I.

##### 6.4.1.3 Analysis of the investigator reported endpoints

SAEs are descriptively reported (frequencies of events and frequencies of patients with any event) by MedDRA SOC and PT.

Adverse events of special interest (pericardial bleedings and pulmonary alveolar bleedings/pulmonary bleedings) are descriptively reported (frequencies of events and frequencies of patients with any event)

Non-serious AEs, are descriptively reported (frequencies only) by MedDRA SOC, outcome of event, reasonable causal relationship to ASA, -clopidogrel, -rivaroxaban and -VKA, and Action taken with ASA, - clopidogrel, -rivaroxaban and –VKA.

#### 6.5 Other analysis

Pre-NOAF and post-NOAF analysis are carried out as an exploratory analysis for the primary efficacy variable (DTE). On treatment, pre-NOAF and post-NOAF analysis are carried out as an exploratory analysis for the primary safety (PBE) variable. The analyses are done analogue to the superiority HR analysis as described in [6.2.1.2](#) and are visualized in [flowchart 4](#).

The separate components of the adjudicated primary efficacy and safety endpoint are analyzed exploratory and analogue to the superiority HR analysis as described in [6.2.1.2](#). The separate components of the adjudicated primary efficacy and safety endpoint are:

- All-cause death
- Any stroke
- Myocardial infarction
- Symptomatic valve thrombosis
- Pulmonary embolism
- Deep vein thrombosis
- Non-CNS systemic embolism
- Life-threatening or disabling bleeds (BARC type 3b, 3c or 5)
- Major bleeds (BARC type 3a).

The following details of NOAF are summarized by treatment:

- Subjects with NOAF reported on ECG but without medication switch
- Subjects with medication switch but without ECG evidence of NOAF
- Subjects with both ECG evidence and medication switch

Medication switch here means: requiring treatment with high dose oral anticoagulation as specified in 3.2.

Mean transaortic valve pressure gradient is measured by echocardiogram (TTE or TEE) at screening and at approximately 360 days after randomization. The difference between 360 days and screening is derived and analyzed exploratory by using a t-test.

The analysis the other variables are visualized in [flowchart 2](#) in appendix I.

## 6.6 Subgroup analysis

The following subgroup variables based on baseline demographics are planned according to the subgroup analysis:

- Region (Northern America, Eastern Europe, Western Europe)
- Sex (male, female)
- Age (< Median, ≥ Median)
- Weight (< Median, ≥ Median)
- BMI (Underweight (<18.5), Normal (≥18.5 & <25), Overweight (≥25 & <30), Obese (≥30))

- Valve type (balloon-expandable, self-expandable)
- Valve-in-valve procedure
- Surgical Risk Scores:
  - Society of Thoracic Surgeons' (STS) risk score (Low (STS<3), Intermediate (3<=STS<=8), High (STS>8))
  - EuroSCORE II (low risk (<5 %), intermediate risk ( $\geq 5\%$  &  $\leq 10\%$ ), high risk (>10%))
- Renal function (Estimated Glomerular Filtration Rate):
  - <30 mL/min/1.73 m<sup>2</sup>
  - $\geq 30$  & <50 mL/min/1.73 m<sup>2</sup>
  - $\geq 50$  & <80 mL/min/1.73 m<sup>2</sup>
  - $\geq 80$  mL/min/1.73 m<sup>2</sup>
- Hypertension (yes, no)
- Diabetes mellitus (yes, no)
- History of a prior stroke (ischemic or unknown type) or non-CNS systemic embolism (yes, no)
- Prior MI (yes, no)
- Previous revascularization (CABG or PCI)
- CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (< Median,  $\geq$  Median)
- HAS-BLED (< Median,  $\geq$  Median)
- TAVR done because of subjects frailty (yes/no)

### 6.6.1 Analysis of the subgroups

Subgroup analysis is done outside the scope of the main analysis.

Subgroups analysis for the primary efficacy and safety variables are based on the ITT data scope. The subgroup analyses are presented descriptively without formal hypotheses testing. Homogeneity of treatment effect in subgroups, both in magnitude and direction, is 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. The following SAS code may be used (using subgroup male as example):

```
proc phreg data= work.infile;  
model d2fDTE * DTE (0)=treat male treat*male;  
run;  
/*  
where  
work.infile = name of source dataset
```



```
treat          = randomization code
DTE            = death and thromboembolic event
d2fDTE        = days to first DTE (since randomization)
male = 1 for male and 0 for female
*/
```

For subgroups the HR per subgroup is derived and the accompanying p-value for interaction. The following SAS code may be used:

```
proc phreg data=work.infile2;
where male = 1;
model d2fDTE*DTE(0) = treat /risklimits;
run;
proc phreg data=work.infile2;
where male = 0;
model d2fDTE*DTE(0) = treat /risklimits;
run;
/*
where
work.infile = name of source dataset
treat       = randomization code
DTE         = death and thromboembolic event
d2fDTE      = days to first DTE (since randomization)
male = 1 for male and 0 for female
*/
```

The p-value for interaction can also be obtained from the first phreg statement in this section (with the interaction term).

A forest plot will be created to visualize the results.

The analysis of the subgroups are visualized in [flowchart 5](#) in appendix I.

As the number of subgroup analyses is 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 variables will be interpreted as “flags” to prompt further investigation. This further investigation may include the likelihood ratio test proposed by Gail and Simon to test for qualitative interaction.<sup>9,10</sup>

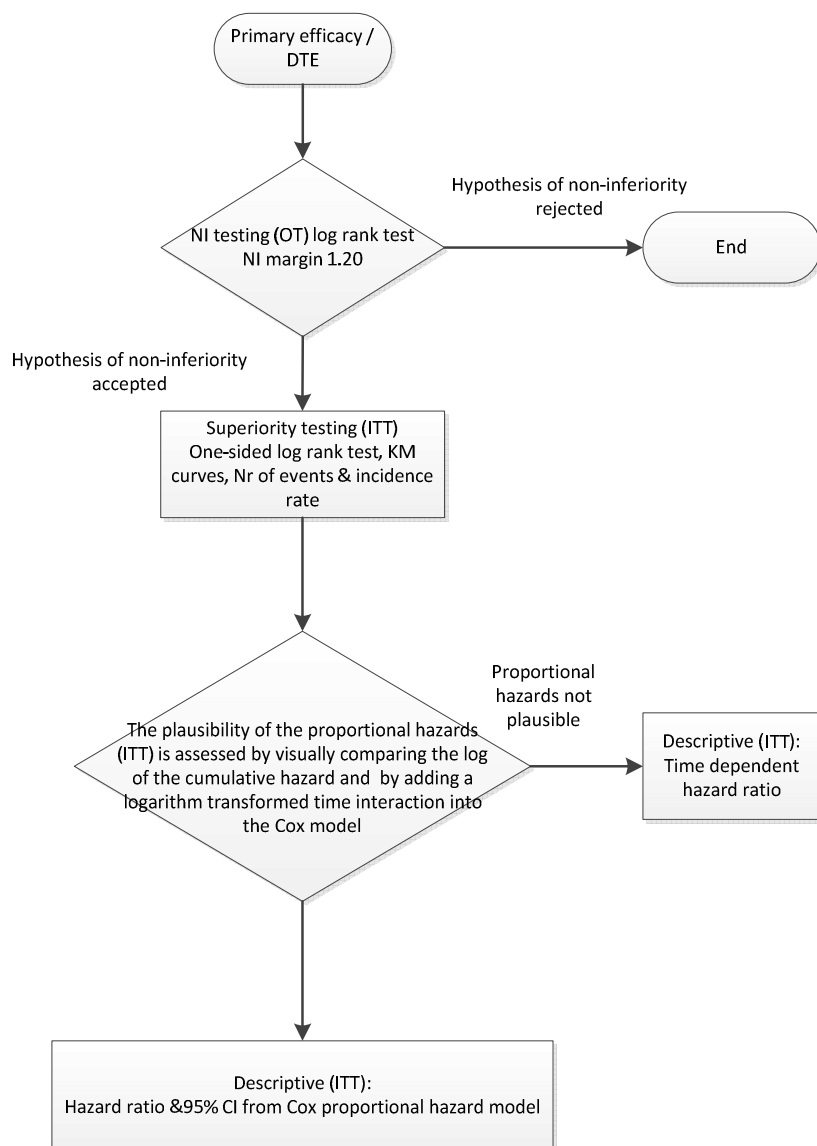


## 7. Document history and changes in the planned statistical analysis

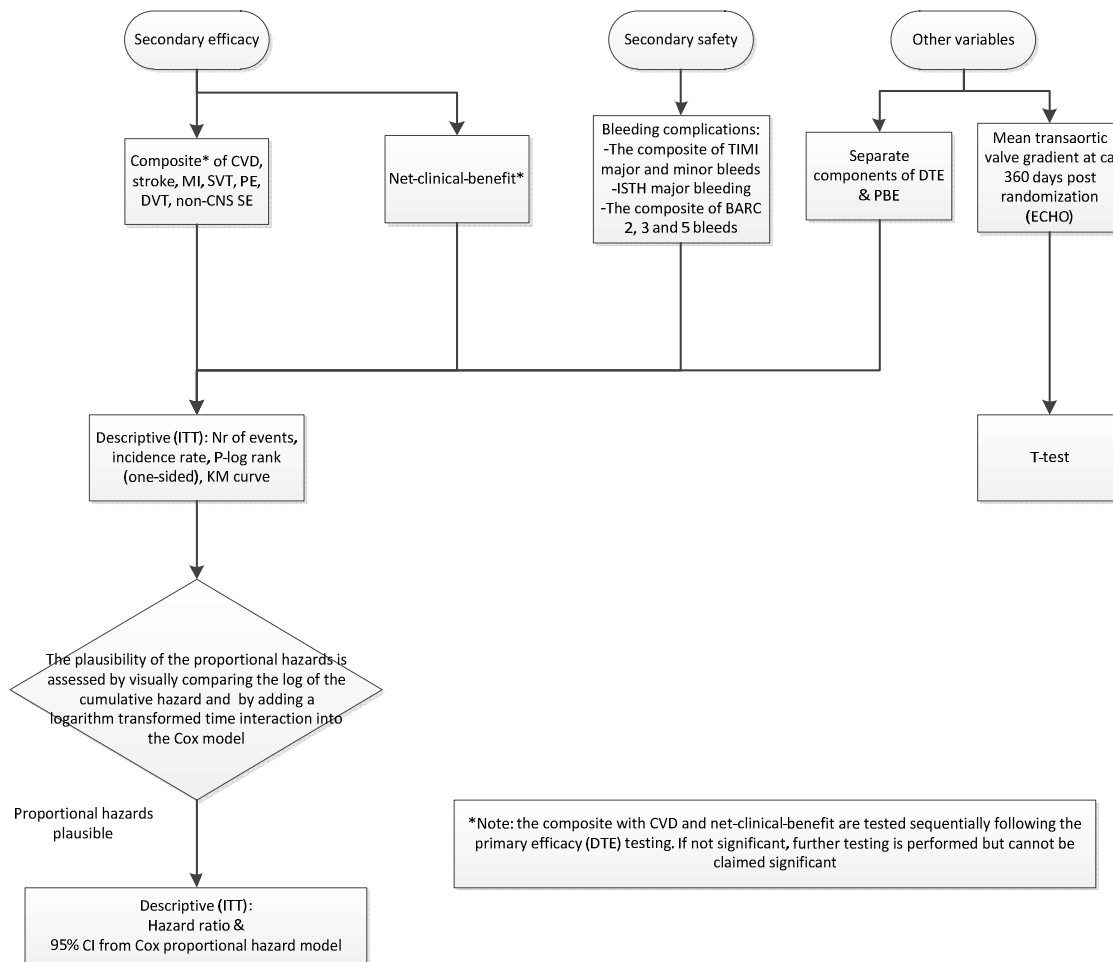
None.

## 8. Appendix I Flowcharts

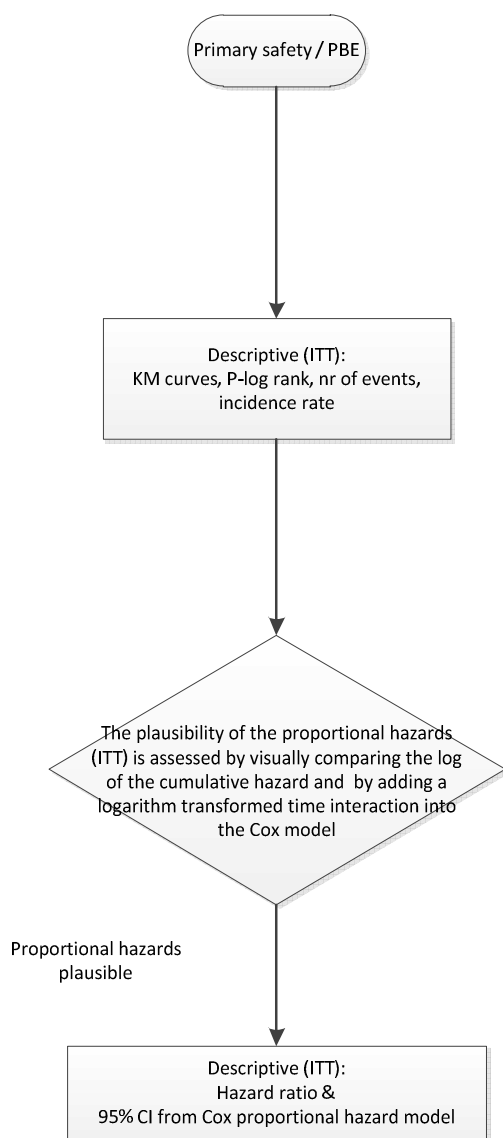
### 8.1 Flowchart 1: Primary efficacy



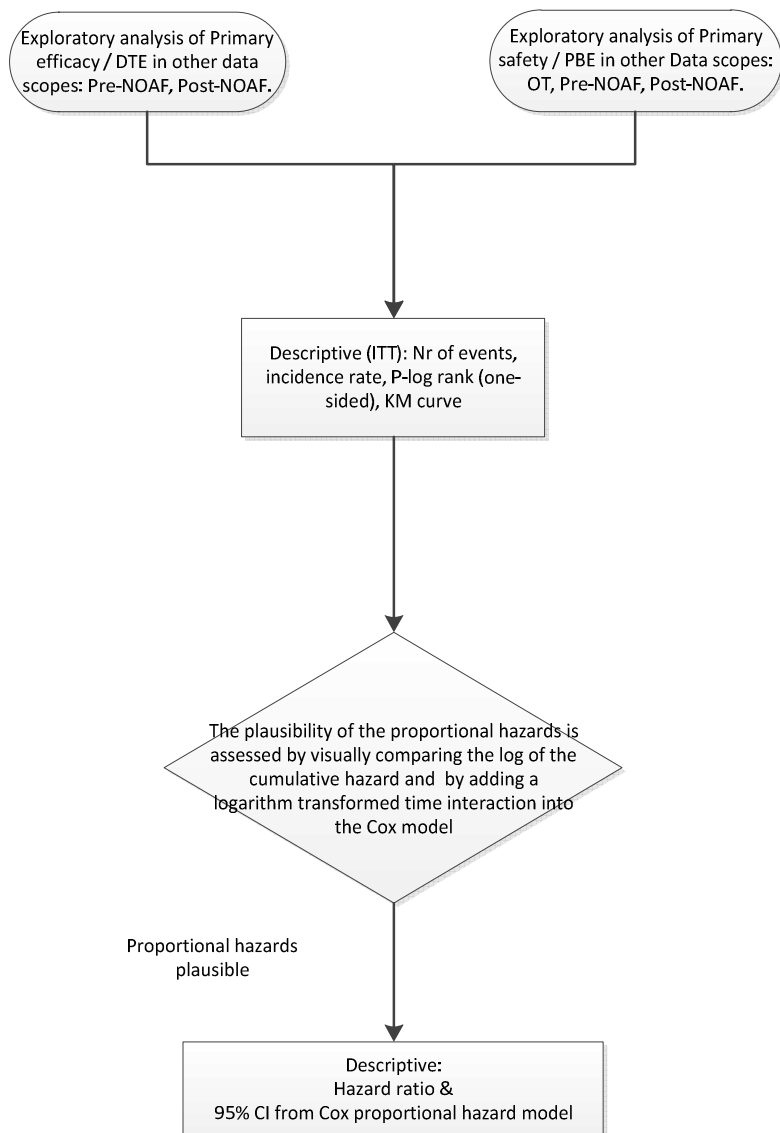
## 8.2 Flowchart 2: Secondary efficacy, secondary safety and other variables



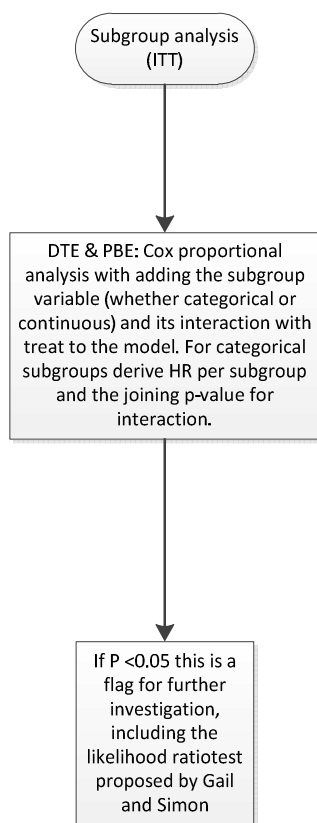
### 8.3 Flowchart 3: Primary safety



## 8.4 Flowchart 4: Primary efficacy and primary safety in other data scopes



## 8.5 Flowchart 5: Subgroups



## 9. References

- <sup>1</sup> Otto CM, Prendergast B. Aortic-valve stenosis--from patients at risk to severe valve obstruction. *N Engl J Med*. 2014;371(8):744-56.
- <sup>2</sup> Amat-Santos IJ, Rodes-Cabau J, Urena M, DeLarochelliere R, Doyle D, Bagur R, et al. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;59(2):178-88.
- <sup>3</sup> Green P, Woglom AE, Genereux P, Daneault B, Paradis JM, Schnell S, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. *JACC Cardiovasc Interv*. 2012;5(9):974-81.
- <sup>4</sup> Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364(23):2187-98.
- <sup>5</sup> Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363(17):1597-607.
- <sup>6</sup> Athappan G, Gajulapalli RD, Sengodan P, Bhardwaj A, Ellis SG, Svensson L, et al. Influence of transcatheter aortic valve replacement strategy and valve design on stroke after transcatheter aortic valve replacement: a meta-analysis and systematic review of literature. *J Am Coll Cardiol*. 2014;63(20):2101-10.
- <sup>7</sup> Tay EL, Gurvitch R, Wijesinghe N, Nietlispach F, Wood D, Cheung A, et al. A highrisk period for cerebrovascular events exists after transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2011;4(12):1290-7.
- <sup>8</sup> Sin-ho Jung, Sun J. Kang, Linda M. McCall & Brent Blumenstein (2005) Sample Size Computation for Two-Sample Noninferiority Log-Rank Test, *Journal of Biopharmaceutical Statistics*, 15:6, 969-979, DOI: 10.1080/10543400500265736
- <sup>9</sup> Gail M., Simon R. Testing for qualitative interactions between treatment effects and patient subsets. *Biometrics*. 1985 Jun, 41(2):361-72.
- <sup>10</sup> Dmitrienko A., Molenberghs G., Chuang-Stein C., and Offen W. *Analysis of Clinical Trials Using SAS: A Practical Guide*. Cary, NC, SAS Institute Inc., 2005