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| **Document Type:** | Study Protocol |
| **Official Title:** | 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. |
| **NCT Number:** | NCT02556203 |
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# Cover page of the integrated protocol

**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.**

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

- **Original protocol,** Version 1.0, dated 25 JUN 2015
- **Amendment 1** (described in Section 15.1)
  forming integrated protocol Version 2.0, dated 28 SEP 2015
- **Amendment 3** (described in Section 15.2)
  forming integrated protocol Version 3.0, dated 17 AUG 2016

**The following local amendment is not part of this integrated global protocol:**

- **Amendment 2 (Norway), dated 16 FEB 2016**

# 1. Title page

**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.**

Acronym GALILEO

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| Test drug: | **BAY 59-7939 / JNJ-39039039 / Rivaroxaban** | | |
| Clinical study phase: | Phase 3 | Date: | 17 AUG 2016 |
| Registration: | 2015-001975-30 | Version no.: | 3.0 |
| Sponsor's study no.: | 17938 | | |
| Sponsor: | **Non-US territory: Bayer AG, D-51368 Leverkusen, Germany**<br>**US territory: Bayer HealthCare Pharmaceuticals Inc.**<br>**100 Bayer Boulevard, PO Box 915, Whippany, NJ 07981-0915 USA** | | |
| Sponsor's medical expert: | PPD<br><br>Rua Domingos Jorge, 1100 – Building 9301, 2nd floor<br>04779-900 São Paulo-SP Brazil<br>Tel: PPD<br>Fax: PPD<br>PPD | | |

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

## Signature of the sponsor's medically responsible person

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

Name: PPD Role: PPD

Date: Signature:

## Signature of principal investigator

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

Name:

Affiliation:

Date: Signature:

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

In the protocol document, this page may remain unsigned.

# 2. Synopsis

*This section was modified by Amendments 1 and 3. For details, please see Sections 15.1 and 15.2.*

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| **Title** | 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. |
| **Short title** | Global study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement to Optimize clinical outcomes. |
| **Acronym** | GALILEO |
| **Clinical study phase** | Phase 3 |
| **Study objective(s)** | 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).<br>To assess the primary bleeding events (PBE) of the rivaroxaban-based strategy, following TAVR, compared to an antiplatelet-based strategy. |
| **Test drug(s)**<br>**Name of active ingredient** | • Rivaroxaban (BAY59-7939 / JNJ-39039039)<br>• Acetylsalicylic Acid (ASA) |
| **Dose(s)** | **Rivaroxaban-based strategy**<br>• Rivaroxaban 10 mg once-daily AND Acetylsalicylic Acid (ASA) 75-100 mg once-daily<br>• Rivaroxaban 10 mg once-daily<br><br>If new-onset atrial fibrillation (NOAF) occurs:<br>• Rivaroxaban 20 or 15 mg once-daily AND ASA 75-100 mg once-daily<br>• Rivaroxaban 20 or 15 mg once-daily |
| **Route of administration** | Oral |

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| **Duration of treatment** | The first dose of rivaroxaban (10 mg once-daily) is started at the time of randomization, if the subject is not on clopidogrel, or within 1-3 days after the last intake of clopidogrel. In case study medication is started the next day post-TAVR, study medication should not be started earlier than the time the TAVR was done on the previous day and the subject should be stabilized and complications or bleedings should have been excluded carefully.<br>Rivaroxaban 10 mg once-daily can be taken with or without food. ASA 75-100 mg once-daily is to be continued unchanged or started immediately after randomization if not already being taken. ASA is discontinued after 90 days from randomization. Rivaroxaban is continued until the efficacy cut-off date, i.e. when the predefined number of efficacy endpoints is reached or earlier if the event rate is unexpectedly low. In the event of NOAF the dose of rivaroxaban is switched from 10 mg once-daily to 20 or 15 mg once-daily, depending on renal function. Rivaroxaban 20 and 15 mg once-daily should be taken with food. Up to 90 days after randomization, ASA 75-100 mg once-daily is to be continued unchanged. After 90 days from randomization, ASA is discontinued and rivaroxaban 20 or 15 mg once-daily is continued alone until the efficacy cut-off date. |
| **Reference drug(s)** | |
| **Name of active ingredient** | • Clopidogrel hydrogen sulfate (clopidogrel)<br>• ASA |
| **Dose(s)** | **Antiplatelet-based strategy**<br>• Clopidogrel hydrogen sulfate (clopidogrel) 75 mg once-daily AND ASA 75-100 mg once-daily<br>• ASA 75-100 mg once-daily<br>If NOAF occurs:<br>• Vitamin K antagonist (VKA) with a target international normalized ratio (INR) 2-3 AND ASA 75-100 mg once-daily<br>• VKA (target INR 2-3) |
| **Route of administration** | Oral |
| **Duration of treatment** | Clopidogrel 75 mg once-daily and ASA 75-100 mg once-daily are to be continued unchanged, or to be started at the time of randomization if not already being taken. In subjects that are |

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| | clopidogrel-naïve at randomization a single loading dose of at least 300 mg clopidogrel should be administered followed by clopidogrel 75 mg once-daily. Clopidogrel must be discontinued at 90 days post-randomization and ASA 75-100 mg once-daily is to be continued until the efficacy cut-off date.<br><br>In the event of NOAF, the antiplatelet-based strategy will be stopped and a VKA with a target INR 2-3 started. ASA 75-100 mg once-daily is to be continued in combination with VKA until 90 days after randomization. After 90 days, ASA must be discontinued and VKA continued alone until the efficacy cut-off date. |
| **Background treatment** | The use of gastric protection drugs that do not interact with cytochrome P450 (CYP) 2C19 (such as pantoprazole) is strongly recommended. |
| **Indication** | Post-successful transcatheter aortic valve replacement (TAVR). |
| **Diagnosis and main criteria for inclusion /exclusion** | Key inclusion criteria:<br>• Successful TAVR of an aortic valve stenosis (either native or valve-in-valve)<br>• By iliofemoral or subclavian access<br>• With any approved/marketed device<br>• Written informed consent (IC)<br><br>Key exclusion criteria:<br>• Atrial fibrillation (AF), current or previous, with an ongoing indication for oral anticoagulant treatment<br>• Any other indication for continued treatment with any oral anticoagulant (OAC)<br>• Known bleeding diathesis (such as but not limited to active internal bleeding, clinically significant bleeding, platelet count ≤ 50,000/$mm^3$ at screening, hemoglobin level < 8.5 g/dL, active peptic ulcer or known gastrointestinal (GI) bleeding, history of intracranial hemorrhage or subdural hematoma)<br>• Any ongoing absolute indication for dual antiplatelet therapy (DAPT) at time of screening that is unrelated to the TAVR procedure<br>• Clinically overt stroke within the last 3 months<br>• Planned coronary or vascular intervention or major surgery |

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| | • Severe renal impairment (eGFR < 30 mL/min/1.73 $m^2$) or on dialysis, or post-TAVR unresolved acute kidney injury with renal dysfunction stage 2 or higher<br>• Moderate and severe hepatic impairment (Child-Pugh Class B or C) or any hepatic disease associated with coagulopathy.<br><br>Screening, IC and randomization:<br><br>Subjects are screened for inclusion after TAVR. Consenting subjects must be randomized within 1-7 days after a successful TAVR and before hospital discharge. |
| **Study design** | Event-driven, randomized, open-label with blinded endpoint evaluation, parallel-group, active-controlled, multicenter, international study |
| **Methodology** | The primary comparison will be to test the superiority of a rivaroxaban-based strategy to an antiplatelet-based strategy with respect to the primary efficacy endpoint. This comparison is preceded by a non-inferiority test that must be satisfied.<br><br>Estimates of the hazard ratio for bleeding events together with their 95% confidence intervals will be calculated for descriptive purposes. |
| **Type of control** | Control treatment strategy is composed of active treatments and is in line with the current standard of care. |
| **Clinical Event Committee** | Yes |
| **Data Safety Monitoring Board** | Yes |
| **Number of subjects** | A total of 1520 subjects will be randomized. |
| **Primary variable(s)** | Primary Efficacy Endpoint: death or first adjudicated thromboembolic event (DTE) defined as the composite of all-cause death and adjudicated any stroke, myocardial infarction (MI), symptomatic valve thrombosis, pulmonary embolism (PE), deep vein thrombosis (DVT), or non-CNS systemic embolism.<br><br>Primary Safety Endpoint: primary bleeding event (PBE) defined as the composite of adjudicated life-threatening, disabling or major bleeding, classified according to the valve academic research consortium (VARC) definitions following the bleeding academic research consortium (BARC) classification. |

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| **Time point/frame of measurement for primary variable(s)** | Subjects are treated and followed from randomization until the study ends, i.e. when the predefined number of primary efficacy endpoints is reached or earlier if the event rate is unexpectedly low and study closure activities are completed. Therefore, the duration of the treatment period for a given subject will depend on the time required to collect these events. The expected duration of the study is 750 days, but depending upon the rate of subject recruitment and endpoint event rates it may be adapted. Regular assessments are planned to take place during the study. |
| **Plan for statistical analysis** | The primary endpoints (for efficacy and for safety) are analyzed as a time-to-event endpoint, in the full analysis set (FAS) of all randomized subjects.<br><br>The primary efficacy endpoint (DTE) is tested for superiority using log-rank test. This test is preceded by a non-inferiority (NI) test with a hazard ratio NI margin at 1.20 using the on-treatment approach. If non-inferiority is met, a test for superiority is performed using the intention-to-treat (ITT) approach. |

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# List of abbreviations

*This section was modified with Amendment 3. For details, see Section 15.2.*

| | |
|---|---|
| ACS | Acute coronary syndrome |
| ACC | American college of cardiology |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AF | Atrial fibrillation |
| AHA | American heart association |
| AKIN | Acute kidney injury |
| APT | Antiplatelet therapy |
| ARO | Academic research organization |
| AS | Aortic stenosis |
| ASA | Acetylsalicylic acid |
| BARC | Bleeding academic research consortium |
| CNS | Central nervous system |
| CVE | Cerebrovascular event |
| COPD | Chronic Obstructive Pulmonary Disease |
| CEC | Clinical Event Committee |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| CTAF | Clinical trial application form |
| CI | Confidence interval |
| CRO | Contract research organization |
| CABG | Coronary artery bypass grafting |
| CAD | Coronary artery disease |
| CIOMS | Council for international organizations of medical sciences |
| CYP | Cytochrome P |
| d | Day(s) |
| DSMB | Data safety monitoring board |
| DTE | Death or first adjudicated thromboembolic event |
| DVT | Deep vein thrombosis |
| DAPT | Dual-antiplatelet therapy |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EOT | End-of-treatment |
| eGFR | Estimated glomerular filtration rate |
| e.g. | Exempli gratia (for example) |
| EMA | European medicines agency |
| et al. | Et alii (and others) |
| etc. | Et cetera (and so on) |
| EU | European union |
| EudraCT | EU data repository for clinical trials |
| FDA | Food and Drug Administration |
| FAS | Full analysis set |
| GEE | Generalized estimation equations |
| GI | Gastrointestinal |
| GP | General practitioner |
| GCS | Global clinical supplies |
| GPV | Global pharmacovigilance |
| GCP | Good clinical practice |
| GMP | Good manufacturing practice |
| h | Hour(s) |
| HIV | Human immunodeficiency virus |
| HR | Hazard ratio |
| IB | Investigator's brochure |
| IC | Informed consent |
| ICH | International Council for Harmonization |
| i.e. | Id est (that is) |
| IEC | Independent ethics committee |
| INR | International normalized ratio |
| IMP | Investigational medicinal product |
| INN | International non-proprietary name |
| ISTH | International Society on Thrombosis and Haemostasis |
| ITT | Intention-to-treat |
| IRB | Institutional review board |
| ISRCTN | International standard randomized controlled trial number register |
| IxRS | Interactive Web or Voice Response System |
| LPLV | Last patient last visit |
| LVEF | Left ventricular ejection fraction |
| ML | maximum partial likelihood method |
| MAR | Medical affairs responsible |
| MedDRA | Medical dictionary for regulatory activities |
| min | Minutes |
| MI | Myocardial infarction |
| NB | Nota bene (note carefully) |
| NI | Non-inferiority |
| NIMP | Non-investigational medicinal product |
| NOAF | New-onset atrial fibrillation |
| NOAC | Non-vitamin K oral anticoagulants |
| NSAID | Non-steroidal anti-inflammatory drugs |
| NVAF | Non-valvular atrial fibrillation |

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| FXa | Factor Xa | od | Once-daily |
| FDAAA | FDA Amendment Act | OAC | Oral anticoagulant |
| PVL | Paravalvular leak | SAC | Statistical analysis center |
| PCI | Percutaneous coronary intervention | SAPT | Single-antiplatelet therapy |
| PK | Pharmacokinetics | STS | Society of Thoracic Surgeons' |
| PDF | Portable data format | SPC | Summary of product characteristics |
| PBE | Primary bleeding event | SAVR | Surgical aortic valve replacement |
| PT | Pro-thrombin time | SUSAR | Suspected unexpected serious adverse reaction |
| PPM | Prosthesis-patient mismatch | TOC | Table of contents |
| PE | Pulmonary embolism | TIMI | Thrombolysis in Myocardial Infarction |
| QA | Quality assurance | THR | Total hip replacement |
| RCT | Randomized control trial | TKR | Total knee replacement |
| RRR | Relative risk reduction | TAVR | Transcatheter aortic valve replacement |
| SAE | Serious adverse event | TIA | Transient ischemic attack |
| SDV | Source data verification | VARC | Valve academic research consortium |
| SOP | Standard operating procedure | VKA | Vitamin K antagonists |
| SAP | Statistical analysis plan | US(A) | United States (of America) |
| SID | Subject identification | | |

# 3. Introduction

Calcific aortic valve stenosis is the most common cause of aortic stenosis (AS) among adults in Europe and in the United States (1). Its pathobiological basis involves chronic valvular tissue inflammation, lipoprotein deposition, osteoblast activation, and extracellular calcifications (2).With a pooled prevalence of 3.4%, the burden of aortic valve stenosis disease among the elderly due to severe aortic stenosis is substantial. Prevalence increases with age, and severe AS, if left untreated, is fatal in a few years from symptom onset. Since no medical treatment has been proven to be effective in severe AS, the treatment of choice has been aortic valve replacement, either by surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) (1-4). Under the current indications, approximately 290,000 elderly patients with severe AS are TAVR candidates in the European countries and in the United States; and nearly 27,000 patients become eligible for TAVR annually (3). The prevalence of moderate or severe AS was found to be age-dependent rising from 0.02% in subjects aged 18–44 years to 2.8% in patients aged ≥ 75 years (4). And it is well recognized that the natural history of mild and moderate AS is also associated with excess mortality and major adverse events (AEs) (4).

Among patients at prohibitive surgical risk, TAVR has become the treatment of choice. The introduction of TAVR has further modified the treatment of high surgical risk patients and based on the available data the indication for TAVR has become a valid alternative to SAVR in patients deemed at intermediate-to-high surgical risk (5-8). The safety and efficacy of TAVR compared with medical management and SAVR has been demonstrated in clinical trials using the two most commonly used TAVR devices, the balloon-expandable Edwards Sapien / SAPIEN XT valve (Edwards Sapien, CA) and the Medtronic CoreValve Revalving System (Medtronic Inc., CA) (6, 7, 9, 10). PARTNER trial cohort B results showed that TAVR improved survival in patients who cannot undergo SAVR compared with medical management. TAVR was also compared with SAVR both, among high-risk patients in the PARTNER trial cohort A, where it was associated with similar rates of survival at 1 year, and among intermediate-to-high-risk patients in the CoreValve trial where a significantly higher rate of survival was observed at 1 year (5-7). Of note, patients undergoing TAVR remain at high-risk of peri- and post-procedural cardiovascular events, mainly strokes, and mortality (11). In high-risk patients receiving TAVR in the PARTNER trial (i.e. cohort A) all-cause mortality was as high as 24% at 1 year, and approximately 34% at 2 years, whereas cardiovascular mortality was 14% and 21%, respectively. The composite of the rate of all-cause death or stroke was 27% and 37% in the TAVR group after 1 and 2 years, respectively (12).

Even though part of the strokes occur during the peri-procedural period, the patients remain at risk of stroke throughout the first months after the procedure (13). Stortecky et al (14) have provided a depiction of the time-dependent risk of strokes after TAVR where the predictors for stroke are considered including new-onset atrial fibrillation (NOAF). NOAF is observed in over 30% of patients undergoing TAVR and has been demonstrated as single, independent predictor of stroke during the subacute phase after TAVR (14). In the PARTNER trial (cohort A, high-risk patients cohort), the rates of stroke remained high amounting to 4.6% at 30 days, 6.0% at 1 year, and 7.7% at 2 years of follow-up (12). Similarly, in the PARTNER trial

(cohort B, inoperable patients cohort) the rate of stroke was 6.7% at 30 days, 11.2% at 1 year, and 13.8% at 2 years of follow-up (15).

Stenotic aortic valves, unlike normal aortic valve leaflets, are characterized by large amounts of tissue factor and thrombin, which might contribute to increased inflammation and thrombogenicity (16). While the diseased aortic valve is resected in case of SAVR before the prosthesis implantation, the pathologic native valve remains in situ in case of TAVR. During both the preparation of the balloon aortic valvuloplasty and the implantation of the TAVR device the diseased native valve may be subject to fractures and injuries, which may induce the exposure and/or embolization of valvular components into the arterial circulation (17, 18). Recently, van Mieghem et al demonstrated that > 50% of cerebral emboli during TAVR are composed of thrombotic material (19). However, also calcific atherosclerotic emboli are common during catheter and device manipulation of a stenotic aortic valve (19). Moreover, the insertion of a prosthesis without removal of the diseased aortic valve creates an irregular zone around the valvular frame that may predispose to thrombus formation. In addition to this pro-thrombotic environment created by the implanted valve, the occurrence of atrial arrhythmias, platelet dysfunction, and associated comorbidities may predispose patients to bleeding or ischemic events. In fact, NOAF as mentioned above is frequently observed following TAVR and has been demonstrated as single, independent predictor of stroke during the subacute phase after TAVR (5, 20-22).

Transcatheter heart valve thrombosis is a rare event but may result in increased transvalvular gradients requiring anticoagulant therapy. One case of transcatheter heart valve thrombosis (0.8%) was reported among the 130 TAVR subjects enrolled in the PARTNER EU trial (23).

Bleeding is a frequent periprocedural complication after TAVR, which has been shown to be associated with worse prognosis (21, 24-28). Although acute and sub-acute post-TAVR bleeding complications (up to 30 days) are linked to procedural or technical factors (e.g., vascular complications (29)), the impact of late bleeding events (after 30 days) in this population is still unclear. Data from the randomized cohorts and continued access registries in the PARTNER trials (27) suggest that major late bleeding complications occur in approximately 6% of patients between 30 days and 1 year, with GI and neurological bleedings being most frequent and are associated with an increased rate of death and morbidity. Independent predictors for late major bleeding events after TAVR included the presence of AF, moderate or severe residual paravalvular leak (PVL), presence of low baseline hemoglobin, and increased left ventricular mass.

Currently, dual-antiplatelet therapy (DAPT) with ASA and mainly clopidogrel for 3 to 6 months (if no indication for anticoagulation is present) is an empirical strategy widely accepted and incorporated as guideline recommendation for patients undergoing TAVR (26, 30-33). However, clopidogrel duration or loading dose is not specifically defined in guidelines, and lately the general usefulness of clopidogrel in combination with ASA in TAVR patients has been questioned (32, 34, 35) . In two small non-randomized studies comparing DAPT to single-antiplatelet therapy (either ASA or clopidogrel), DAPT did not reduce the rate of cerebrovascular events but was associated with a higher rate of major and life-threatening bleeding complications (34, 36).

Since it is unclear whether thrombi produced during and after TAVR have a platelet- or thrombin-based origin, an antiplatelet-based strategy alone may not be the optimal treatment in these patients. Controversy also exists for patients with a history of pre-existing atrial fibrillation. There are only individual reports on treatment with triple therapy (37) and no evidence regarding warfarin with one antiplatelet or warfarin alone and the American and Canadian guidelines discourage the use of triple therapy (31, 35). Therefore triple therapy after TAVR should be avoided in patients with a high inherent bleeding risk. The combination of one oral anticoagulant with one antiplatelet has resulted in better safety results, without excess ischemic events, in comparison to triple therapy in AF patients undergoing PCI (36, 38). Thus, to date the optimal strategy and pharmacological treatment to reduce the long-term thromboembolic risk after TAVR is unknown. In fact, as the current antithrombotic management during and after TAVR is not based on randomized controlled clinical trials but only on consensus, there is an unmet need to identify the best antithrombotic treatment in patients without AF undergoing TAVR.

Consequently, non-vitamin K oral anticoagulants (NOAC) such as rivaroxaban may potentially reduce the TAVR-related thrombogenicity without increasing the bleeding risk.

## 3.1. Population demographics in TAVR

Patients undergoing TAVR are mostly octo-/nona-genarians with approximately 50% being female. Comorbid conditions are frequent and include congestive heart failure (uniformly), AF in one third of patients, severe chronic obstructive lung disease in 14% of patients, coronary artery disease in 70% of patients, renal impairment in close to 80% of patients, peripheral vascular disease in 30% of patients, and concomitant mitral regurgitation in 30% of patients (39). However, recent evidence points to a change in clinical practice with many more patients at intermediate risk undergoing TAVR and with a corresponding decline in procedural complications and improved clinical outcomes. Propensity-score matched comparisons between TAVR and conventional SAVR in patients at intermediate risk suggest similar survival (few years horizon) (40), and currently two prospective randomized trials directly compare TAVR with SAVR in intermediate risk patients (41, 42). Owing to the rapid progress in transcatheter valve technology with improved procedural success and low rates of paravalvular aortic regurgitation, it is anticipated that the indication of TAVR will continue to widen.

Important clinical considerations in a TAVR population include age, gender, renal impairment, atrial fibrillation, congestive heart failure class, and established coronary or vascular atherosclerosis. Clinical decision-making often relies on a subject's absolute risk of a disease event of interest. However, in a frail population, competing risk events may preclude the occurrence of the event of interest and defaulting to all-cause (rather than specific etiology related) mortality appears well substantiated in this patient population.

## 3.2. Rivaroxaban

Rivaroxaban (BAY 59-7939, JNJ-39039039) is a potent and highly selective oral direct factor Xa inhibitor. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation, and development of thrombi (43). Of the administered dose, approximately 2/3 undergoes metabolic degradation, with half then

being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion. The elimination half-life is 5 - 9 hours in young individuals, and 11 - 13 hours in the elderly. Plasma concentrations correlate with the prothrombin time and the activated partial thromboplastin time (43).

Please refer to the latest available version of the investigator's brochure (IB) (44) for further comprehensive information regarding rivaroxaban.

## 3.3. Previous studies with rivaroxaban

**Preclinical and clinical studies**

- Rivaroxaban has been tested in a wide range of dose levels and is approved in various indications across distinct areas of use: DVT/PE prophylaxis (VTE prevention in Orthopedic surgery): 10 mg orally once-daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-4) (45-48).

  The REgulation of Coagulation in major ORthopedic surgery to prevent DVT and PE (RECORD) program was the first phase III program initiated in support of the clinical development of the first indication for rivaroxaban, the prevention of venous thromboembolic disease in patients undergoing major orthopedic surgery such as total hip (THR) or total knee (TKR) replacement. Rivaroxaban 10 mg once-daily was significantly more effective than enoxaparin in the prevention of VTE after THR and TKR with similar bleeding rates in the RECORD program.

- Venous thromboembolism (VTE) treatment and prevention of recurrent DVT and PE: 15 mg orally twice-daily for three weeks followed by 20 mg orally once-daily (EINSTEIN DVT, EINSTEIN PE) (49, 50) or 20 mg orally once-daily (EINSTEIN Extension) to reduce the risk of recurrence of DVT/PE.

- Non-valvular AF: 20 or 15 mg once-daily depending on renal function was able to reduce the risk of stroke or non-CNS systemic embolism in patients with non-valvular AF (ROCKET AF) (51-53).

  ROCKET AF (Rivaroxaban Once-daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation) was the first phase III study with rivaroxaban for the indication of stroke prevention in atrial fibrillation. ROCKET AF, a randomized, double-blind, double-dummy, event-driven study, in which 14,264 subjects with non-valvular atrial fibrillation were randomized to receive either once-daily rivaroxaban or warfarin. Subjects with a history of prior ischemic stroke, transient ischemic attack (TIA), or systemic embolism, or 2 or more of the following risk factors: heart failure and/or left ventricular ejection fraction (LVEF) $\leq$ 35%, hypertension, age $\geq$ 75 years, or diabetes mellitus were randomized to either rivaroxaban 20 mg once-daily (reduced dose of 15 mg once-daily for subjects with moderate renal impairment at baseline) or dose-adjusted warfarin (target INR 2-3). Overall, in ROCKET AF, active treatment with rivaroxaban was non-inferior to warfarin for the primary composite endpoint of stroke or non-CNS systemic embolism, a comparable rate of major and non-major clinically relevant bleeding, and a significantly lower rate of intracranial hemorrhage (51).

- Secondary prevention of acute coronary syndromes (ACS): In ATLAS ACS (54, 55) Rivaroxaban 2.5 mg twice-daily in combination with ASA ± clopidogrel or ticlopidine reduced the risk of recurrence of atherothrombotic events in patients after an ACS with elevated cardiac biomarkers.

## 3.4. Dose rationale

This will be the first study investigating rivaroxaban for prevention of cardiovascular events in subjects who underwent a successful TAVR.

Based on the reasons outlined below, it is anticipated that the 10 mg once-daily dose of rivaroxaban, when used in combination with ASA for the first 90 days and thereafter alone without antiplatelet therapy, will provide an adequate efficacy and an acceptable safety (bleeding) profile compared to standard of care in this population:

i. In the ROCKET AF study, treatment with rivaroxaban 20 mg once-daily was non-inferior to warfarin in terms of prevention of stroke or non-CNS systemic embolism in the ITT population and was superior in the safety on-treatment population. There was no significant between-group difference in the risk of major bleeding. Importantly, intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.
ii. However, the 20 mg once-daily dose, especially when administered in combination with ASA, is considered too high in the TAVR population with increased risk of bleeding where the optimal balance between benefit and risk is crucial. Warfarin, when compared to ASA, is more efficacious in patients with non-valvular atrial fibrillation (NVAF) (relative risk reduction [RRR] 39%) (56), but may increase bleeding. Thus, testing a dose lower than 20 mg of rivaroxaban not only may reveal a relevant efficacy benefit, but it may also provide an improved safety profile in terms of bleeding. This is important as the current standard of care used in TAVR patients is DAPT for 3 - 6 months after the TAVR procedure followed by single antiplatelet therapy lifelong, which has a lower risk for bleeding. Based upon these considerations, there is a strong argument to use a rivaroxaban dose lower than 20/15 mg for patients without established indication for anticoagulation in this study.
iii. The 10 mg once-daily dose of rivaroxaban is deemed to demonstrate the best benefit-risk balance considering the high risk of bleeding and the comparator being DAPT in the first 90 days after TAVR followed by single antiplatelet therapy. Rivaroxaban will be administered in addition to single antiplatelet therapy with ASA during the first 90 days post-TAVR and thereafter alone without antiplatelet therapy.
iv. The 10 mg once-daily rivaroxaban dose is approved and is shown to be efficacious and safe in VTE prevention in major orthopedic surgery.
v. Simulations showed that plasma concentrations of a 10 mg once-daily dose of rivaroxaban in elderly patients with renal impairment were within the variability range confidence interval of the average patient, suggesting that at this dose all these influencing factors should not lead to significant alterations in rivaroxaban (predicted $C_{max}$ of rivaroxaban for all patients was within the $5^{th}$–$95^{th}$ percentile ranges calculated for the average patient in the population).
vi. Efficacy of rivaroxaban in the elderly patients was similar to observations in younger patients with smaller differences at lower rivaroxaban concentrations but with a

favorable benefit-risk profile in all age groups. The differences in plasma concentrations of rivaroxaban in the elderly are mainly due to reduced renal clearance but, because the dose selected for this study is already a downward adjustment from the dose used for stroke prophylaxis in NVAF, an additional dose adjustment for patients with moderate to severe renal impairment is not considered necessary. Furthermore, for the rivaroxaban dose of 10 mg once-daily, approved for the prevention of VTE in major orthopedic surgery patients, no dose adjustment in normal to moderate renal impairment is required.

vii. While the proposed study will enroll subjects without previous AF post-TAVR, a considerable proportion of patients will develop NOAF after the TAVR procedure and it is currently unknown whether this incidence is underestimated. While subjects without previous AF will receive rivaroxaban 10 mg once-daily post-TAVR, the 20/15 mg once-daily dose tested in the moderate to high risk AF patients in ROCKET AF is considered to be necessary once the patient develops NOAF after the TAVR procedure. Patients who develop NOAF after randomization will therefore be switched to the 20/15 mg once-daily dose of rivaroxaban.

Overall, a 10 mg once-daily dose of rivaroxaban is believed to be the optimal treatment regimen to balance benefit-risk in patients after a TAVR implantation currently treated with antiplatelets. The 20 mg/ 15 mg once-daily dose of rivaroxaban is anticipated to be needed for efficacy only if the patient develops manifest AF after the TAVR implantation.

**Rationale of the study**

Calcific aortic valve stenosis is characterized by an increased thrombogenic and inflammatory profile (2). Long-term oral antithrombotic treatment after TAVR aims to prevent complications, notably ischemic stroke and MI as well as thrombo-embolism 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 AF may occur in about one-third of patients referred for TAVR (20).

Therefore, the actual standard of care after TAVR, i.e. DAPT, is not optimal in targeting the underlying pathophysiological mechanisms in severe AS. Rivaroxaban, through the inhibition of the pathways underlying the increased thrombogenicity, may effectively prevent thrombotic complications after TAVR without exposing this elderly (57) population to an increased bleeding risk.

Stroke and 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 (5, 7, 11). Approximately half of the strokes at 30 days occur within the first 24 hours (13).

The investigation of anticoagulation in the medical management of patients following TAVR is further justified by the fact that the incidence of 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 (20). 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 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.

# 4. Study objectives

## 4.1. Primary objective(s)

*This section was modified with Amendment 3. For details, see Section 15.2.*

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.

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.

## 4.2. 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).

## 4.3. 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 ischemic and thromboembolic complications 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.

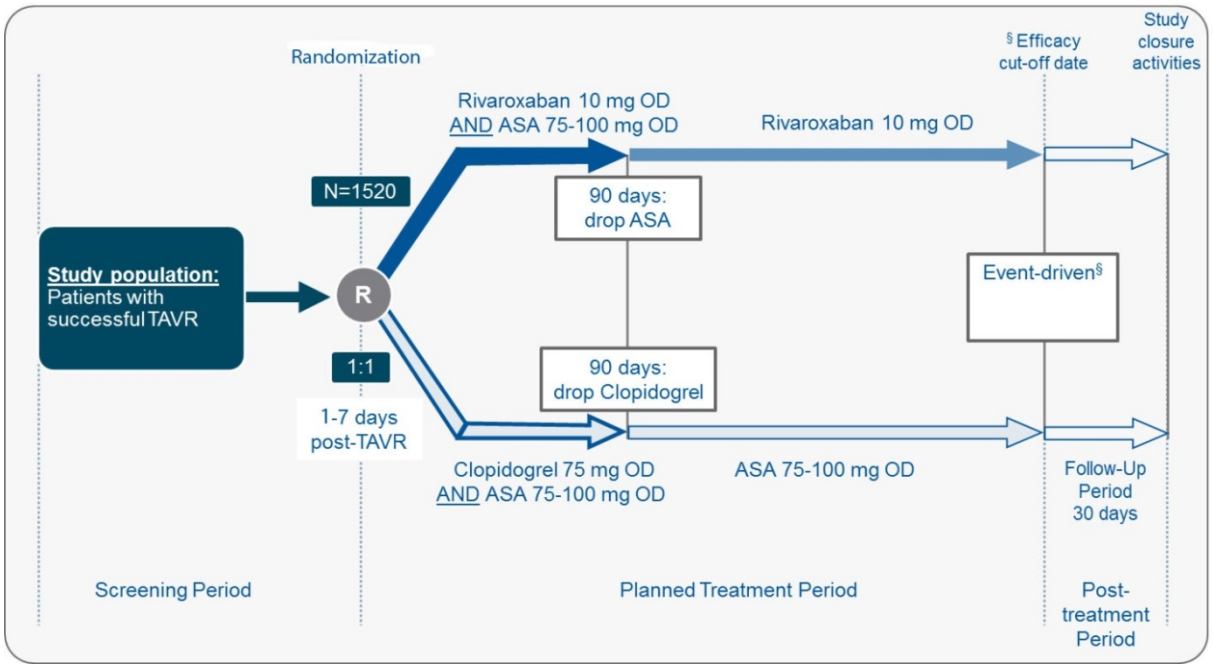
# 5. Study design

## 5.1. Study flow diagram

*The study flow diagram was modified with Amendment 3. For details, see Section 15.2.*

The study design is detailed in Figure 1 Study flow diagram.

**Figure 1: Study flow diagram**




Successful transcatheter aortic valve replacement (TAVR) as defined in Section 6.1.
§ 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.

## 5.2. Study plan

*This section was modified with Amendment 3. For details, see Section 15.2.*

This is an event-driven, randomized, open-label with blinded endpoint evaluation, parallel-group, active-controlled, multicenter, international 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) by iliofemoral or subclavian access with any approved/marketed device type available in the participating countries are potentially eligible for inclusion in the study. 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. The investigator must inform each subject before signature of IC of the aspects of premature withdrawal from the study including the retention and use of all collected data until the end of study as described in Section 6.3 and 13.3.

Randomization must take place within 1-7 days post-TAVR and before hospital discharge. Randomization is performed by an Interactive Web or Voice Response System (IxRS) and stratified by site. Stratification by site is performed to ensure balance across potential local differences in treatment practices.

The assigned treatment strategy is implemented after randomization (please refer to Section 7.4).

Subjects randomized to rivaroxaban-based strategy: In the rivaroxaban-based strategy, rivaroxaban is started at the time of randomization if the subject is not on clopidogrel. If the subject is treated with clopidogrel, clopidogrel is stopped immediately after randomization and rivaroxaban is started within 1-3 days after the last intake of clopidogrel. In case study medication is started the next day post-TAVR, study medication should not be started earlier than the time the TAVR was done on the previous day and the subject should be stabilized and complications or bleedings should have been excluded carefully. Rivaroxaban 10 mg once-daily can be taken with or without food. ASA 75-100 mg once-daily is continued unchanged or started immediately after randomization if not already being taken.

Subjects randomized to antiplatelet-based strategy: In the antiplatelet-based strategy clopidogrel 75 mg once-daily and ASA 75-100 mg once-daily are to be continued unchanged, or to be started at the time of randomization if not already being taken. If clopidogrel is started at the time of randomization in a clopidogrel-naïve subject, a single loading dose of at least 300 mg should be administered followed by clopidogrel 75 mg once-daily.

For both strategies, the selection of the ASA dose (75-100 mg) is left at the discretion of the treating physician. In case the ASA dose before randomization was > 100 mg once-daily, the dose has to be decreased to 75-100 mg once-daily immediately 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 is to be continued. Whereas, in the antiplatelet-based strategy, clopidogrel must be discontinued after 90 days and ASA is to be continued.

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 (Section 9.2.3). 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 ≥ 30 mL/min/1.73m$^2$).

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 (please refer to Section 9.1).

All randomized subjects must be followed until the efficacy cut-off date. Study closure activities should be completed for all randomized subjects, including those that for any reason did not take the assigned study medication, or prematurely discontinued study medication, or have developed either NOAF or any type of efficacy or safety endpoint. All this information must be captured in the eCRF. Every effort should be made to maintain a subject's follow-up compliance. As per agreement, contacting the subject's general practitioner or referring cardiologist should be considered in case the subject cannot be reached in order to obtain information about the subject's health status (especially regarding endpoints occurrence), and should be documented in the electronic case report form (eCRF). Death registry databases or other publicly available sources should be consulted by the sites according to availability and local applicable laws. If explicitly requested by the subject on-site visits may be replaced by telephone contacts.

Study assessments are performed according to the visit scheme provided under Section 9.1. The subject treatment flow diagram (Figure 2) is depicted in this same section.

## 5.3. Study variable(s)

### 5.3.1. Primary variable(s)

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 primary safety endpoint is primary bleeding event (PBE), defined according to VARC definitions following the BARC classification as the adjudicated composite of:

- life-threatening bleed
- disabling bleed
- major bleed

The endpoint definitions and the definitions of terms are located in Sections 16.1 and 16.2, respectively. Acronyms and abbreviations are defined in the List of abbreviations.

### 5.3.2. Secondary variable(s)

The secondary endpoints include:

- The adjudicated composite of cardiovascular 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).

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 bleeding

### 5.3.3. Other variable(s)

*This section was modified with Amendment 3. For details, see Section 15.2.*

The individual components of the primary efficacy and safety endpoint will be assessed as other endpoints.

The mean transaortic valve pressure gradient at approximately 360 days after randomization as measured by routine echocardiogram (TTE or TEE), if available, will be captured in the eCRF and it is considered as an exploratory study endpoint.

**End of study**

The end of the study as a whole will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries.

The primary completion event for this study occurs when the 440th subject experiences a positively adjudicated primary efficacy endpoint or earlier if the event rate is unexpectedly low. The efficacy cut-off date is defined as the date of the primary completion event.

For practical purposes, the anticipated efficacy cut-off date is set based on a projection of the date of the primary completion event before 400 subjects have experienced a positively adjudicated primary efficacy endpoint. When the anticipated efficacy cut-off date is set, on-site visit will be scheduled for all subjects within 6 weeks.

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

# 6. Study population

*This section was modified with Amendment 3. For details, see Section 15.2.*

## 6.1. Inclusion criteria

Potential subjects must satisfy the following criteria to be enrolled in the study:

- Man or woman of 18 years of age or older
- Have a successful TAVR of an aortic valve stenosis (either native of valve-in-valve)
- Via iliofemoral or subclavian access
- With any approved/marketed TAVR device
- Provide written IC

**Successful TAVR (29) is defined:**

1. Correct positioning of a single prosthetic heart valve into the proper anatomical location.
2. Intended performance of the prosthetic heart valve - presence of all 3 conditions post-TAVR:
   a. mean aortic valve gradient < 20 mmHg
   b. peak transvalvular velocity (aortic valve maximum velocity) < 3.0 m/s
   c. no severe or moderate aortic valve regurgitation
3. Absence of periprocedural complications, such as:
   a. Any type of periprocedural stroke
   b. VARC graded life-threatening bleeding
   c. Acute coronary artery obstruction requiring intervention

d. Major vascular complication requiring intervention (including access-site vascular complications, any new ipsilateral peripheral ischemia, distal embolization from a vascular source, aortic dissection, aortic rupture, ventricular perforation, cardiac tamponade, and annulus rupture)

e. Unresolved acute valve thrombosis

f. Any requirement of a repeat procedure

## 6.2. Exclusion criteria

Subjects are NOT eligible to participate in this trial if they meet ANY of the following exclusion criteria:

**General**

1. Any atrial fibrillation (AF), at the time of randomization or previous, with an ongoing indication for oral anticoagulant treatment
2. Any other indication for continued treatment with any oral anticoagulant (OAC)

**Bleeding risks or systemic conditions**

3. Known bleeding diathesis, such as but not limited to:
   a. active internal bleeding, clinically significant bleeding, bleeding at a non-compressible site, or bleeding diathesis,
   b. platelet count $\leq 50{,}000/mm^3$ at screening
   c. hemoglobin level < 8.5 g/dL
   d. history of intracranial hemorrhage or subdural hematoma
   e. major surgery, biopsy of a parenchymal organ, or serious trauma within 30 days before randomization
   f. active peptic ulcer or known upper GI bleeding within the last 3 months

**Concomitant and study medication**

4. Any ongoing absolute indication for dual-antiplatelet therapy (DAPT) at time of screening that is unrelated to the TAVR procedure
5. Known hypersensitivity or contraindication to acetylsalicylic acid, clopidogrel or rivaroxaban or hypersensitivity to contrast media that could not be solved neither by switching to an alternate contrast media nor with pre-treatment with appropriate medication
6. Routine use of oral non-steroidal anti-inflammatory drugs (NSAID)
7. Concomitant therapy with systemic drugs that are strong inhibitors of both CYP 3A4 and P-gp (azole antimycotics such as ketoconazole and itraconazole or HIV protease inhibitors such as ritonavir)
8. Concomitant therapy with drugs that are strong CYP 3A4 inducers (e.g. carbamazepine, phenytoin, rifampin, St. John’s wort)

9. Concomitant therapy with omeprazole or esomeprazole that cannot be switched to an alternate medication.

**Concomitant conditions**

10. Planned coronary or vascular intervention or major surgery
11. Clinically overt stroke within the last 3 months
12. Severe renal impairment (eGFR < 30 mL/min/1.73 $m^2$) or on dialysis, or post-TAVR unresolved acute kidney injury with renal dysfunction stage 2 or higher
13. Moderate and severe hepatic impairment (Child-Pugh Class B or C) or any hepatic disease associated with coagulopathy
14. Active infective endocarditis
15. Active malignancy (diagnosed within 5 years) except for adequately treated non-melanoma skin cancer or other non-invasive or in situ neoplasm (e.g., cervical cancer in situ that has been successfully treated or non-active prostate cancer)

**Other exclusion criteria**

16. Dementia or forgetfulness hindering compliance with medication intake or other study procedures
17. Legally incompetent to provide IC
18. Previous (30 days before enrolment) or concomitant participation in another clinical study with investigational medicinal product(s).
19. Previous assignment to treatment during this study
20. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site) or sponsor
21. Female of childbearing potential
    a. Who are not surgically sterile, or who are sexually active and not willing to use adequate contraceptive measures with a failure rate less than 1% per year (e.g. oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, male partner sterilization) before entry and throughout the study, or
    b. For whom a negative pregnancy test is unavailable before study entry, or
    c. Who are pregnant or breast feeding before study entry.

## 6.3. Withdrawal of subjects from study

All subjects will be encouraged to remain under observation for the full duration of the study. However, at any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

It is important though, to note that discontinuation of the assigned study treatment strategies is not equivalent to withdrawal of IC.

Moreover, withdrawal of IC does not mean withdraw of permission to collect further information. In whether this refers to permanent discontinuation or interruption of the assigned therapy (the most common expected scenario), unwillingness to attend on-site 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. general practitioner) is to be assessed by the investigator. See Section 6.3.1.2 for detailed information on withdrawal of IC.

The reason for withdrawal (e.g. lost-to-follow-up, withdrawal of consent, protocol violation, AE, efficacy outcome reached, or subject unable/unwilling to comply with study medication, etc.) must be recorded in the eCRF and in the subject's medical records.

In all cases, every effort must be made to continue to follow the subject and survival status information must be determined for all randomized subjects by the end of the study.

## 6.3.1. Withdrawal

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 will be performed.

### 6.3.1.1. Discontinuation of treatment

Neither erroneous randomization of subject in the presence of exclusion criteria or non-fulfilment of inclusion criteria nor a post-randomization change in health status that results in the subject meeting one or more of the exclusion criteria should not automatically lead to the interruption or permanent discontinuation of the assigned therapies, unless continuing the medications places the subject at undue risk as determined by the investigator. Such situations though very rare, may occur and should be handled on a case-by-case basis.

#### 6.3.1.1.1. Temporary discontinuation of assigned therapy

Study assigned therapies may be temporarily discontinued however these interruptions should be kept to a minimum. Subjects should resume the assigned therapy as soon as the treating physician considers it safe to do so. During and after a temporary discontinuation, subjects will continue to undergo on-site visits and phone assessments and the timing of such visits should if possible remain the same. If the subject cannot return for an on-site visit, a telephone assessment will be performed.

The reason for temporary discontinuation of the assigned therapy must be recorded in the eCRF and in the subject's medical records. Please refer to Section 8.1 for other potential reasons for interruption of the assigned therapies.

If an invasive procedure or surgical intervention is required, rivaroxaban 10/15/20 mg once-daily should be stopped at least 24 hours before the intervention, if possible, and based on the clinical judgment of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention. Rivaroxaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate hemostasis has been established and the treating physician considers it safe to do so.

The management of subjects assigned to the antiplatelet-based strategy in need of an invasive procedure or clinical intervention is at the discretion of the treating physician. It is advised that the summary of product characteristics as well as the appropriate local and national guideline recommendations are followed.

For clinically significant bleeding events, the assigned study medication may be temporarily stopped to allow its management. The decision to restart or permanently withdraw study medication after resolution of a bleeding event is at the discretion of the investigator.

#### 6.3.1.1.2. Permanent discontinuation of assigned therapy

Any subject who discontinues prematurely the assigned study medication after he/she has been randomized with no intention to restart is defined as having a permanent discontinuation. Study assessments must be continued according to the visit scheme provided under Section 9.1 and the subject treatment flow diagram.

The reason for a permanent discontinuation must be recorded in the eCRF and in the subject's medical records. Study medication assigned to the discontinued subject must not be assigned to another subject.

The assigned therapy must be subject of a permanent discontinuation for any of the following reasons:

- If any AE occurs which is not acceptable in the opinion of the investigator and/or participating subject
- Continuous treatment is required with an excluded medication for the remaining duration of the study
- Calculated CrCl declines below 30 mL/min on 2 consecutive occasions (control within 24 hours) or subject requires dialysis
- Non-compliance with the study medication regimen in the judgment of the investigator
- Pregnancy (as confirmed by serum or urine pregnancy test)
- Development of hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk in the judgment of the treating physician

It is noted however, that permanent discontinuation of the assigned therapy is discouraged wherever possible. If a subject early permanently discontinues the assigned therapy, clinical follow-up should be continued until the efficacy cut-off date.

In case of permanent discontinuation of the assigned therapy in a subject randomized to the rivaroxaban-based strategy, ASA 75-100 mg once-daily for the remaining duration of the study is recommended if the treating physician considers it safe and the clinical situation allows doing so.

### 6.3.1.2. Withdrawal of IC

A subject may withdraw the IC and still allow further release of information. In this situation, the subject’s consent to the collection of further data should be documented in the site’s

source documents.

Clinical follow-up should be considered unless the subject explicitly refuses any type of collection of information.

The following possibilities may be observed if a subject withdraws consent:

1. Collection of further information allowed
2. Collection of vital status only allowed
3. Collection of further information not allowed

1. Withdrawal of consent and collection of further information allowed:

Follow-up data will be collected for these subjects and it is imperative to obtain complete data including information on efficacy and safety endpoints, whether or not they receive the assigned therapy.

For patients who do not agree to attend regular study visits, the scheduled visits can be performed by phone and the investigator will encourage the patient to return to the clinic for at least one final on-site visit once the anticipated efficacy cut-off date is set in order to perform all assessments as outlined.

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

For subjects who withdraw IC with collection of further information allowed, the investigator should continue to conduct clinical follow-up contacts according to the schedule of evaluations (see details Section 9.1 and Figure 2) until the efficacy cut-off date. The information to be obtained at each subject contact remains as described under the standard Visit description (Section 9.2). At a minimum, the following information should be obtained and documented in the eCRF for subjects who withdrawal consent with collection of further information allowed:

- Vital status
- Efficacy and safety endpoints
- NOAF assessment
- SAEs

2. Withdrawal of consent and collection of vital status only allowed:

For subjects who withdraw consent for release of information, vital status only should be obtained. The measures taken for follow-up must be documented in the source data.

Vital status should be obtained when the anticipated efficacy cut-off date is set.

3. Withdrawal of consent and collection of further information not allowed:

In cases where subjects indicate they do not want to be contacted to collect vital status, the withdrawal of consent must be made separately as described under Section 13.3.

In this instance, all collected data so far remain in the study database.

#### 6.3.1.3. Lost-to-follow-up

In case a subject is identified as potential lost-to-follow-up, every possible effort must be made by study site personnel to contact the subject and obtain complete data while determining the reason for withdrawal from the study.

At a minimum, the following information should be obtained and documented in the eCRF for subjects' lost-to-follow-up:

- Vital status
- SAEs
- Efficacy and safety endpoints

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12.

### 6.3.2. Replacement

A study subject that has been withdrawn from the study will not be replaced.

## 6.4. Subject identification

The subject identification (SID) is a 9 digit number consisting of:

Digits 1 to 2 = Country code

Digits 3 to 5 = Center number within the country

Digits 6 to 9 = Current subject number within the center

The SID numbers must be used in sequence and no number should be skipped, substituted, or re-used.

Registration of the screening will be performed via a central web-based system. The IxRS will be filled by each investigational site, and the system will allocate to the subject a unique ID number.

# 7. Treatment(s)

## 7.1. Treatments to be administered

*This section was modified by Amendment 1. For details, see Section 15.1.2.2.*

Study treatment assignment will be open-label. Study treatments consist of rivaroxaban and in addition of the standard of care treatments clopidogrel, ASA, and VKA, which are systematically prescribed to TAVR subjects in accordance to the relevant guidelines and routine clinical practice (8, 30, 33).

Eligible study subjects will be randomized in a ratio of 1:1 to one of the 2 following treatment arms:

### 7.1.1. Rivaroxaban-based strategy (experimental strategy)

*This section was modified with Amendment 3. For details, see Section 15.2.*

**Drugs:**

- Rivaroxaban 10 mg once-daily
- Acetylsalicylic Acid (ASA) 75-100 mg once-daily
  - First 90 days:
    - Rivaroxaban 10 mg once-daily AND ASA 75-100 mg once-daily

      The first dose of rivaroxaban is given at the time of randomization if the subject is not on clopidogrel or within 1-3 days after the last intake of clopidogrel. In case study medication is started the next day post-TAVR, study medication should not be started earlier than the time the TAVR was done on the previous day and the subject should be stabilized and complications or bleedings should have been excluded carefully. ASA 75-100 mg once-daily is continued unchanged or started immediately after randomization if not already being taken.

      The selection of the ASA dose (75-100 mg) is left at the discretion of the treating physician. In case the ASA dose before randomization was > 100 mg once-daily, the dose has to be decreased to 75-100 mg once-daily immediately after randomization.
  - After the first 90 days:
    - Rivaroxaban 10 mg once-daily alone.
    - ASA 75-100 mg once-daily is discontinued.

#### 7.1.1.1. After NOAF

- First 90 days:
  - Rivaroxaban 20 mg once-daily OR 15 mg once-daily for subjects with moderate renal impairment (i.e. eGFR < 50 and ≥ 30 mL/min/1.73m$^2$, estimated by the MDRD formula)
  - ASA is continued unchanged, as 75-100 mg once-daily.
- After the first 90 days:
  - Rivaroxaban 20 mg once-daily OR 15 mg once-daily for subjects with moderate renal impairment (i.e. eGFR <50 and ≥ 30 mL/min/1.73 m$^2$). Rivaroxaban is continued alone.
  - ASA 75-100 mg once-daily is discontinued.

### 7.1.2. Antiplatelet-based strategy (control strategy)

**Drugs:**

- Clopidogrel hydrogen sulfate (i.e. Clopidogrel) 75 mg once-daily
- ASA 75-100 mg once-daily
  - First 90 days:
    - DAPT: clopidogrel 75 mg once-daily AND ASA 75-100 mg once-daily

      In subjects that are clopidogrel-naïve at randomization a single loading dose of at least 300 mg clopidogrel should be administered followed by clopidogrel 75 mg once-daily.

      The choice of P2Y12 inhibitor should follow the current TAVR guidelines and recommendations (32, 33, 35).

      The selection of the ASA dose (75-100 mg) is left at the discretion of the treating physician. In case the ASA dose before randomization was > 100 mg once-daily, the dose has to be decreased to 75-100 mg once-daily immediately after randomization.
  - After the first 90 days:
    - ASA 75-100 mg once-daily alone.
    - Clopidogrel 75 mg once-daily is discontinued.

#### 7.1.2.1. After NOAF

- First 90 days:
  - Open-label VKA therapy to target INR 2-3, according to guidelines.

- Clopidogrel 75 mg once-daily is discontinued.
- ASA 75-100 mg once-daily is continued unchanged.

- After the first 90 days:
  - Open-label VKA therapy alone to target INR 2-3.
  - Clopidogrel 75 mg once-daily must remain discontinued.
  - ASA 75-100 mg once-daily is discontinued.

Initiation of VKA therapy will be performed according to the summary of product characteristics (SPC) or relevant product label for the respective VKA. INR values will be measured according to local standard of practice. The investigator should assess if a parenteral anticoagulant drug (such as low molecular weight heparin) for bridging purposes is needed in addition to VKA therapy as per standard of care until the target INR of at least 2.0 is achieved.

In case NOAF is diagnosed and the patient refuses to switch to the full oral anticoagulation as described above (whether rivaroxaban 20/15 mg once-daily in the rivaroxaban-based strategy or VKA in the antiplatelet-based strategy), the patient may remain on the study treatment assigned before NOAF for the remaining duration of the study if the treating physician considers it safe and the clinical situation allows doing so (58, 59).

In case atrial flutter is diagnosed after randomization with an ongoing indication for full oral anticoagulant treatment, the choice of the full anticoagulation should follow the treatment recommendation for NOAF as per the assigned treatment strategy and described above.

## 7.2. Identity of study treatment

*This section was modified by Amendment 1. For details, see Section 15.1.2.3.*

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

A system of numbering in accordance with all requirements of good manufacturing practice (GMP) will be used, ensuring that each dose of rivaroxaban can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance (QA) group.

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

### 7.2.1. Rivaroxaban

*This section was modified by Amendment 1. For details, see Section 15.1.2.4.*

Xarelto® (rivaroxaban, BAY59-7939) will be provided by Bayer as film coated immediate release tablets containing 10 mg, 15 mg or 20 mg of rivaroxaban in high-density polyethylene (HDPE) bottles. Tablets are for oral use. Rivaroxaban is part of the rivaroxaban-based treatment strategy.

### 7.2.2. Clopidogrel, ASA and VKA

*This section was modified by Amendment 1. For details, see Section 15.1.2.5.*

Clopidogrel, ASA and VKA will be supplied from local investigative centers' resources and will be used according to the product labeling for the approved formulations. If required by local regulations, Bayer will purchase these drugs from local commercial sources, and label and distribute to the investigational site.

## 7.3. Treatment assignment

Randomization will be performed via a central IxRS with stratification by investigational site. The randomization scheme will be securely stored at the statistical department of the database management center.

Each investigational site will enter the IxRS and fill in relevant subject details needed to randomize the subject. Based on this information, the system will assign a unique treatment number for that subject. Subjects will be randomly assigned in a 1:1 ratio to receive a rivaroxaban-based strategy or an antiplatelet-based strategy. This is an open-label trial and once subject is assigned to a treatment arm, no treatment cross-over is permitted.

## 7.4. Dosage and administration

The selection of the treatment doses as described in Section 7.1 above have been justified under Section 3.4.

Study medication should be taken at approximately the same time each day throughout the study (approximately 24 hours apart).

During the study, study drug will be dispensed at appropriate intervals, as depicted in the Tabular schedule of evaluations (Section 9.1), to ensure subjects have adequate quantities of study drug between study visits. Subjects should be advised to finish taking all the pills in one bottle before starting the next one.

The planned duration of the treatment period for a given subject will vary depending on the rate of subject recruitment and actual event rates.

## 7.5. Blinding

This trial is an open-label trial and therefore both investigators and study subjects are aware of the treatment arm assigned.

## 7.6. Drug logistics and accountability

*This section was modified by Amendment 3. For details, see Section 15.2.*

Rivaroxaban will be stored at the investigational site in accordance with GCP and GMP requirements and according to the instructions given by the clinical supplies department of the sponsor (or its affiliate/CRO/academic research organization [ARO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of

receipt, the responsible site personnel will confirm receipt of rivaroxaban via IxRS. The study personnel will use rivaroxaban only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of rivaroxaban must be properly documented according to the sponsor's agreed and specified procedures. Re-supply of rivaroxaban is automatically initiated through the IxRS module in the eCRF.

The drug accountability process is described in further detail separately in the Monitoring Manual. Written instructions on medication destruction will be made available to the affected parties as applicable.

## 7.7. Treatment compliance

### 7.7.1. Rivaroxaban

Study personnel will maintain a log of all rivaroxaban dispensed. Drug supplies for each subject will be inventoried and reconciled throughout the study. Any discrepancies between actual and expected amount of returned study medication must be discussed with the subject at the time of the visit, and any explanation must be documented in the source records and captured in the eCRF.

Subjects will return empty study drug containers and unused study drug at those visits when a new supply of rivaroxaban is to be received.

During the treatment period, the subject will be provided with sufficient medication to cover the period until the next on-site visit.

If a dose is missed the subject should take rivaroxaban immediately and continue on the following day with the once-daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Subjects should report any missed doses at each on-site visit or telephone assessment. These data will be collected in the eCRF. It is understood that subjects may occasionally miss a dose or that a subject may be placed on temporary discontinuation (see Section 6.3.1.1.1) but this should be avoided or at least kept to a minimum.

### 7.7.2. Clopidogrel, ASA and VKA

Prescribed units of clopidogrel, ASA, and VKA will be recorded in the eCRF. Subjects will be queried on general drug adherence. It is understood that subjects may occasionally miss a dose or that a subject may be placed on temporary discontinuation (see Section 6.3.1.1.1).

# 8. Non-study therapy

## 8.1. Prior and concomitant therapy

*This section was modified with Amendment 3. For details, see Section 15.2.*

All ongoing medications at screening and used during the study (prescription and over-the-counter), including adjunct therapy or medical devices, will be recorded in the appropriate

section of the eCRF throughout the study. Use of ASA and clopidogrel or any other P2Y12 inhibitor prior and during TAVR procedure should also be recorded.

It is advised that the appropriate local and national guideline recommendations are followed for any concomitant medications.

The concomitant medication should be evaluated when considering AE causal relationship (Section 9.6.1.2).

Use of medications listed below is allowed with the following restrictions:

- ASA doses >100 mg once-daily after randomization may be used on a temporary basis, but should be avoided for chronic use during the study if possible. If analgesics are required use of paracetamol/acetaminophen are recommended.
- Non-steroidal anti-inflammatory drugs (NSAIDs) may be used on a temporary basis, but should be avoided for chronic use during the study if possible. If analgesics are required use of paracetamol/acetaminophen are recommended.
- Medicines that reduce gastric acid (e.g., H-2 antagonists or proton pump inhibitors [PPIs]) may reduce the incidence of GI bleeding in subjects' post-TAVR who are treated with antithrombotics and unless contraindicated their use is recommended. The choice of gastric protection drugs (such as pantoprazole) is at the discretion of the treating physician. PPIs that interact with cytochrome P450 2C19 (such as omeprazole or esomeprazole) are disallowed in the antiplatelet-based strategy, during concomitant use of clopidogrel.

Concomitant use (with study treatment strategies) of the following therapies is disallowed during the study:

- Single or dual antiplatelet therapy other than assigned study strategy
- VKA other than the assigned study strategy and low molecular weight or unfractionated heparin if used for reasons other than short-term bridging of VKA therapy until the target INR is established
- Factor IIa inhibitors and factor Xa inhibitors other than the study medication
- In the rivaroxaban-based strategy concomitant use of
    - P2Y12 inhibitors in combination with rivaroxaban
    - During concomitant use of rivaroxaban systemic treatment with drugs that are strong inhibitors of both CYP 3A4 and P-gp (azole antimycotics such as ketoconazole and itraconazole or HIV protease inhibitors such as ritonavir). The azole antimycotic fluconazole, a moderate CYP 3A4 inhibitor, has however less effect on rivaroxaban exposure and can be co-administered.
    - During concomitant use of rivaroxaban systemic treatment with drugs that are strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's wort)

- In the antiplatelet-based strategy concomitant use of
    - P2Y12 inhibitor for > 3 months (> 90 days) after randomization
    - Omeprazole or esomeprazole that cannot be switched to an alternative medication during concomitant use of clopidogrel

The prohibited therapies may be administered on a temporary basis provided the study drug is (temporarily) discontinued first but should be avoided whenever possible. Study drug may be restarted after the prohibited therapy has been discontinued and after completion of a suitable washout period at the investigator's discretion (see Section 6.3.1.1.1). The sponsor (or its affiliate/CRO) must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are co-administered.

### 8.2. Post-study therapy

After the anticipated efficacy cut-off date is set and an on-site visit is completed, there will be an observation period to follow subjects in the transition from study treatment strategies to an appropriate therapy, as per the clinical site standard of care. This post-study therapy should also be recorded in the eCRF.

## 9. Procedures and variables

### 9.1. Tabular schedule of evaluations

*This section was modified with Amendment 3. For details, see Section 15.2.*

**Table 1: Schedule of evaluations**

| **Visit number** | | **1** | **2** | **3** | **4** | **5** | **6, 7, (n)** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Screening** | | **Planned treatment** | | | | | | **Post-treatment** |
| **Visit** | **Screening** | **Baseline / Randomization[b]** | **On-site visit** | **On-site visit** | **Phone call** | **On-site visit** | **On-site visit** | **On-site visit** | **Phone call** |
| **Day** | **1-7 days [a] post-TAVR** | **0** | **30** | **90** | **180 [c]** | **360 [c]** | **540,720[c], z** | | |
| | | | | | | | **every 180d** | **EOT [d]** | **EOT+30d [e]** |
| **Window (day[s])** | | | **± 7d** | **± 15d** | **± 15d** | **± 30d** | **± 30d** | **[d]** | **± 7d** |
| **Study Assessments** | | | | | | | | | |
| Informed consent [a] | X | | | | | | | | |
| Demographics [f] | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Prior medication | X | | | | | | | | |
| TAVR assessment | X | | | | | | | | |
| In /exclusion criteria | X | X | | | | | | | |
| Concomitant medication | | X | X | X | X | X | X | X | X |
| Physical exam [p] | | X | X | X | | X | X | X | |
| Vital signs [g] | | X | X | X | | X | X | X | |
| Echocardiogram (TTE or TEE) [h] | X | | | | | X | | | |
| 12-lead ECG | | X | X | X | | X | X | X | |
| **Study Medication** | | | | | | | | | |
| Prescribing/dispensing assigned strategy | | X [i] | X | X | | X | X | | |
| Treatment strategy adjustment [j] | | | | X | | | | | |
| Transition to other therapy | | | | | | | | X | |

| **Visit number** | | **1** | **2** | **3** | **4** | **5** | **6, 7, (n)** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Screening** | | **Planned treatment** | | | | | | **Post-treatment** |
| **Visit** | **Screening** | **Baseline / Randomization[b]** | **On-site visit** | **On-site visit** | **Phone call** | **On-site visit** | **On-site visit** | **On-site visit** | **Phone call** |
| **Day** | **1-7 days [a] post-TAVR** | **0** | **30** | **90** | **180 [c]** | **360 [c]** | **540,720[c], z** | | |
| | | | | | | | **every 180d** | **EOT [d]** | **EOT+30d [e]** |
| **Window (day[s])** | | | **± 7d** | **± 15d** | **± 15d** | **± 30d** | **± 30d** | **[d]** | **± 7d** |
| **Laboratory Assessments (local labs)** | | | | | | | | | |
| Hematology [k] | X | | | | | | | | |
| Liver tests [L] | X | | | | | | | | |
| Renal function [m] | X | | | | | | | | |
| **Ongoing study assessments** | | | | | | | | | |
| Efficacy endpoints | | X | X | X | X | X | X | X | X |
| Safety endpoints | | X | X | X | X | X | X | X | X |
| NOAF assessment and adjustment of treatment [n] | | X | X | X | X | X | X | X | X |
| (Serious) AEs [o] | X | X | X | X | X | X | X | X | X |
| Vital status | | | | | | | | | |

[a] Consenting subjects must be randomized within 1-7 days post-TAVR and before hospital discharge.

[b] Once randomized, a subject has entered the study and all randomized subjects will be followed until the efficacy cut-off date when the predefined number of efficacy endpoints is anticipated or earlier if the event rate is unexpectedly low, even if they did not take assigned study medication or prematurely discontinued study medication. In case of early permanent discontinuation of study medication, all relevant information must be captured in the eCRF as soon as possible after stopping the assigned study medication. The timing of on-site visits and of telephone contacts must be kept unchanged.

[c] The study is event-driven and the number of visits will depend on when the anticipated efficacy cut-off date is set. Subject contacts are planned to take place at 30, 90, and 180 days after randomization and from 180 days onward every 180 days until the anticipated efficacy cut-off date is set.

[d] All randomized subjects must continue clinical follow-up until the anticipated efficacy cut-off date is set, i.e. when the sponsor informs each investigational site to schedule an on-site visit within 6 weeks. If study assigned medication was taken as planned, this assessment coincides with the EOT visit.

[e] A telephone assessment is planned 30 days (±7 days) after a permanent discontinuation of the assigned study medication for all randomized subjects.

[f] Demographics: year of birth, sex and race/ ethnicity, if allowed per local regulations.

[g] Vital signs: blood pressure, heart rate, weight, and height. Note that height only needs to be determined at screening.

[h] The mean transaortic valve pressure gradient post-TAVR should be determined, if available, from either routine transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) recordings and captured in eCRF before discharge and at 360 days after randomization according to local standard of care for TAVR. An echocardiogram at 360 ± 30 days after randomization is preferred. However, if unavailable last available between 180-360 days after randomization can be considered.

[i] The first study drug administration.

[j] Adjust treatment strategy as described in section 7.1 (in the rivaroxaban-based strategy, ASA is discontinued and in the antiplatelet-based strategy, clopidogrel is discontinued).

[k] Hematology tests include hemoglobin, platelet count and white cell count.

[L] Liver tests include transaminases (AST/ALT), total bilirubin and its components (conjugated and/or unconjugated fractions) in case of elevated total bilirubin, and alkaline phosphatase, if available as current standard of care. Liver test results collected before TAVR procedure can be used as long as performed as part of the standard of care for the index-TAVR procedure.

[m] Renal function will be estimated by creatinine clearance (CrCl). The creatinine clearance will be estimated by the MDRD formula using serum creatinine levels.

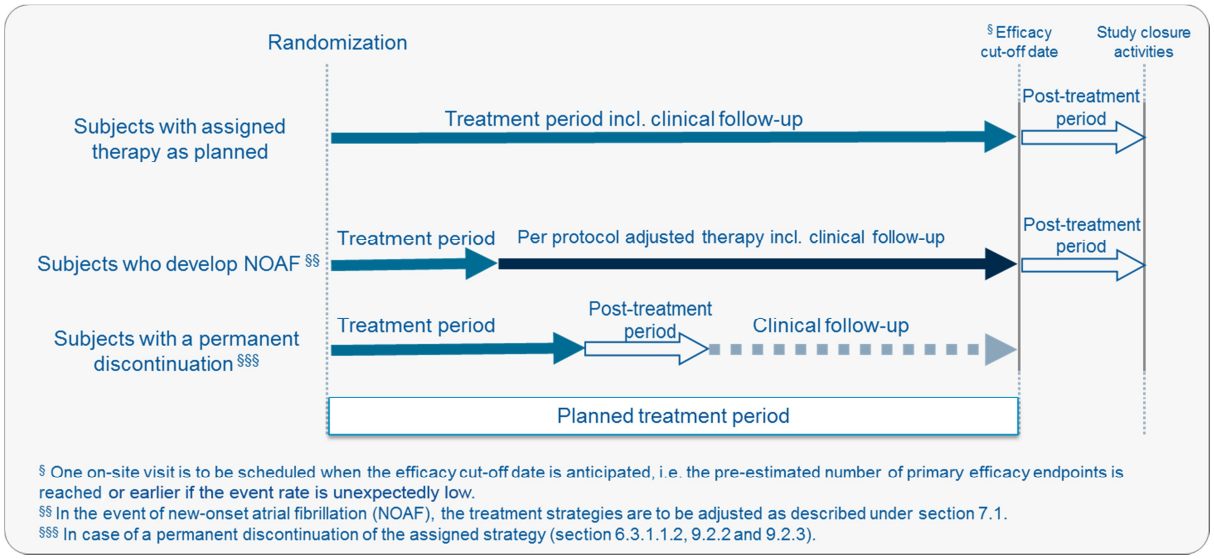
[n] In case of NOAF after randomization subjects in: (a) the rivaroxaban-based treatment strategy will be switched to rivaroxaban 15 or 20 mg once-daily, based on kidney function. eGFR will be used as reported in lab printouts or calculated from serum creatinine levels using the MDRD formula. Subjects with moderate renal impairment and eGFR < 50 and ≥ 30 mL/min/1.73m$^2$ will received an adjusted dose of rivaroxaban of 15 mg once-daily. Both of these doses must be taken with food. (b) Subjects in the antiplatelet-based treatment strategy will switch to vitamin K antagonist after INR assessment (INR target 2-3). These subjects must return for an unscheduled visit as described under section 13.3.

[o] For details, see Section 9.6.1.4 and 9.6.1.6. Only SAEs, AE of special interest (even if classified as non-serious), or AEs that lead to permanent discontinuation of the assigned study medication are to be reported. The investigator must report immediately (within 24 hours of the investigator's awareness) all (S)AEs as described in Figure 3.

[p] Physical examination aims to investigate any occurrence of a safety or efficacy outcome.

AEs, adverse events; EOT, end-of-treatment; d, days; ECG, electrocardiogram.

**Figure 2: Study treatment flow diagram.**




## 9.2. Visit description

The study will be conducted in 3 phases: a screening period (including screening and baseline/randomization), a planned treatment period (consisting of on-site visits and telephone assessment), and a post-treatment observational period. If not stated otherwise, the measures listed in the following section will be performed by or under the supervision of the investigator.

### 9.2.1. Screening period (screening and randomization)

*This section was modified with Amendment 3. For details, see Section 15.2.*

Before any study specific screening examinations take place, potentially eligible subjects will be given a full explanation as to what the study would involve, both verbally and in writing in the form of a written subject information sheet (refer to Section 13.3 for details). Study specific screening examinations will **only** be performed **after** having received the subject's written IC. Please note that if screening procedures are performed as part of routine medical practice (e.g. laboratory parameters) these are not required to be repeated as long as they meet the protocol requirements described below.

Hematology tests and renal function results from standard of care can be used as long as collected after the index-TAVR procedure and before randomization. Liver test results collected before TAVR procedure can be used as long as performed as part of the standard of care for the index-TAVR procedure. Before the IC form is obtained the inclusion and exclusion criteria are reviewed to assess the subjects' eligibility.

If the subject meets all of the inclusion and none of the exclusion criteria, and IC has been obtained, he/she is eligible to be randomly assigned (1:1) to receive either a rivaroxaban-based strategy or an antiplatelet-based strategy and, therefore, should be randomized.

Randomization by IxRS, must take place within 1-7 days post-TAVR, and before hospital discharge. The allocated treatment strategy is implemented after randomization.

If allowed by the subject or for local legal requirements, his/her general practitioner (GP) will be informed of the subject's participation in the trial by means of a letter from the investigator. Information will be included on the treatment strategies as well as on specific clinical assessments that must come to the attention of the investigational study center before subject's treatment is modified (such as, if NOAF is detected).

**Screening (1-7 days post-TAVR)**

The following procedures will be performed 1-7 days after the index-TAVR and **prior to randomization**:

- Obtainment of written IC
  NB: No screening procedures may be performed unless written IC has been obtained.
- Eligibility check (in- and exclusion criteria)
- Register the screening in IxRS (the IxRS system will allocate the subject a unique ID number (refer to Section 6.4 for details)
- Demographic data check
- Medical history
- Prior medication
- TAVR assessment
- Laboratory assessments (see Section 9.6.3.1)
- Routine echocardiogram (TTE or TEE) post-TAVR and before hospital discharge if available per local standard of care for TAVR.

**Visit 1 – Baseline / Randomization**

- Reconfirmation of eligibility (in- and exclusion criteria)
  NB: No subject may be randomized unless adherence to all selection criteria as given in section 6 is established.
- Concomitant medication check
- Physical examination
- Vital signs
- 12-lead electrocardiogram (ECG) or any other method documenting heart rhythm (e.g. ECG strip) able to exclude atrial fibrillation
- Randomization via IxRS (see Section 7.3)

The following procedures will be performed 1-7 days after the index-TAVR, **after randomization and before discharge**:

- First administration of assigned treatment strategy, including instructions on the use of study's treatment strategies
- Continuous assessment of (S)AEs
- Assess if any efficacy and/or safety endpoints occurred
- Assess if NOAF occurred

### 9.2.2. Planned treatment period

*This section was modified with Amendment 3. For details, see Section 15.2.*

The duration of the planned treatment period for a given subject will depend on the time needed to reach the efficacy cut-off date, i.e. to collect the predefined number of primary adjudicated efficacy endpoints in the total study population or earlier if the event rate is unexpectedly low. The expected duration of the treatment period is 720 days but may be longer or even shorter depending upon the rate of subject recruitment and efficacy event rates. Visits are scheduled at 30, 90, 180 days after randomization, and every 180 days thereafter until the anticipated efficacy cut-off date is set (see Section 9.1 Tabular schedule of evaluations Table 1) at which time a final on-site visit will be scheduled. Once notified, the study center must contact each randomized subject and schedule this visit within 6 weeks. Subjects must continue to take their study medication until they return for this on-site visit.

Subjects, who have a permanent discontinuation of study medication, will be also followed between randomization and the visit scheduled after the anticipated efficacy cut-off date is set, unless the subject has withdrawn his/her IC without allowing collection of further information. For more details, please refer to Section 6.3.1.2 and 13.3.

**Visit 2 - On-site visit: 30 days (± 7 days)**

The following procedures will be performed during this on-site visit:

- Concomitant medication check
- Physical examination
- Vital signs check
- 12-lead electrocardiogram (ECG)
- Continuous assessment of (S)AEs
- Assess if any efficacy and/or safety endpoints occurred
- Assess if NOAF occurred
- Prescription of assigned therapy and rivaroxaban dispensation, as needed

**Visit 3 - On-site visit: 90 days (± 15 days)**

The following procedures will be performed during this on-site visit:

- Concomitant medication check
- Physical examination

- Vital signs check
- 12-lead electrocardiogram (ECG)
- Continuous assessment of (S)AEs
- Assess if any efficacy and/or safety endpoints occurred
- Assess if NOAF occurred
- Adjust treatment strategy as described in Section 7.1 (rivaroxaban-based strategy, ASA is discontinued; antiplatelet-based strategy, clopidogrel is discontinued)
- Prescription of assigned therapy and rivaroxaban dispensation, as needed

**Visit 4 - Telephone assessment: 180 days (± 15 days)**

The following procedures will be performed during this telephone contact:

- Concomitant medication check
- Continuous assessment of (S)AEs
- Assess if any efficacy and/or safety endpoints occurred
- Assess if NOAF has been diagnosed

**Visit 5 - On-site visit: 360 days (± 30 days)**

The following procedures will be performed during this on-site visit:

- Concomitant medication check
- Physical examination
- Vital signs check
- 12-lead electrocardiogram (ECG)
- Continuous assessment of (S)AEs
- Assess if any efficacy and/or safety endpoints occurred
- Assess if NOAF occurred
- Prescription of assigned therapy and rivaroxaban dispensation, as needed
- Routine echocardiogram (TTE or TEE) approximately at 360 days after randomization if available per local standard of care for TAVR.

  NB: An echocardiogram at 360 ± 30 days after randomization is preferred. However, if unavailable last available echocardiogram between 180-360 days after randomization can be considered.

**Visit 6 – On-site visit: 540 days (± 30 days)**

The following procedures will be performed during this on-site visit:

- Concomitant medication check

- Physical examination
- Vital signs check
- 12-lead electrocardiogram (ECG)
- Continuous assessment of (S)AEs
- Assess if any efficacy and/or safety endpoints occurred
- Assess if NOAF occurred

**Visit 7 through Visit n - On-site visit: 720 days and every 180 days (± 30 days)**

The following procedures will be performed during this on-site visit:

- Concomitant medication check
- Physical examination
- Vital signs check
- 12-lead electrocardiogram (ECG)
- Continuous assessment of (S)AEs
- Assess if any efficacy and/or safety endpoints occurred
- Assess if NOAF occurred

**Unscheduled on-site visit - NOAF-related**

In the event of NOAF after randomization, the assigned therapy should be modified as defined per protocol (Section 7.1) and the following procedures should be performed during the unscheduled on-site visit:

- Concomitant medication check
- Physical examination
- Vital signs check
- 12-lead electrocardiogram (ECG)
- Continuous assessment of (S)AEs
- Assess if any efficacy and/or safety endpoints occurred
- For subjects in the rivaroxaban-based strategy:
    - Assess creatinine clearance
    - Dispense dose of rivaroxaban according to 7.1.1.1
- For subjects in the antiplatelet-based strategy:
    - Subjects will be transitioned to an open-label vitamin K antagonist (VKA) strategy according to 7.1.2.1 and to the appropriate local guidelines

- Assess INR to adjust dose to target INR 2-3. It is recommended to monitor INRs at least every 4 weeks but the frequency of INR monitoring is left to the discretion of the treating physician.

**On-site visit: EOT**

This visit takes place as soon as possible after the last intake of the assigned study medication.

All subjects must complete this visit to the exception of those with full withdrawal of IC (see Section 6.3.1.2).

The following procedures will be performed during this on-site visit:

- Concomitant medication check
- Physical examination
- Vital signs check
- 12-lead electrocardiogram (ECG)
- Continuous assessment of (S)AEs
- Assess if any efficacy and/or safety endpoints occurred
- Assess if NOAF occurred
- Subject transition from assigned study therapy to an appropriate therapy as per the clinical site standard of care.

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.

Subjects with an early permanent discontinuation of the assigned therapy will be also followed between randomization and the visit scheduled after the anticipated efficacy cut-off date is set, unless the subject opposes by withdrawing the IC and not allowing collection of further information. For this, he/she needs to sign a corresponding declaration of objection; alternatively, the subject's oral objection may be documented in the subject's source data. For more details, please refer to Section 13.3.

### 9.2.3. Post-treatment period

*This section was modified with Amendment 3. For details, see Section 15.2.*

After the last dose intake of the study assigned medication, there will be an observation period to follow subjects after transition from study treatment strategies to an appropriate therapy, as per the clinical site standard of care. All subjects will have a telephone assessment after 30 days (±7 days) including the subjects who had an early permanent discontinuation of the study treatment strategies. For recommendations on the appropriate therapy in case of early permanent discontinuation of the study treatment strategies, please see Section 6.3.1.1.2.

**Telephone assessment: permanent discontinuation of assigned strategy + 30d (±7 days)**

The following procedures will be performed during this telephone contact:

- Medication check
- Continuous assessment of (S)AEs
- Assess if any efficacy and/or safety endpoints occurred
- Assess if NOAF has been diagnosed

**End of study visit**

This visit takes place within 6 weeks of the announcement of the anticipated efficacy cut-off date.

This visit will be performed for subjects who early permanent discontinue the study medication and had the expectation to keep the regular scheduled visits as planned by the time of study drug discontinuation. This visit will also be performed for subjects who withdraw consent and allow collection of further information.

The following procedures, if applicable, will be performed during this visit:

- Assess if any efficacy and/or safety endpoints occurred
- Vital status
- Assessment of (S)AEs

## 9.3. Population characteristics

### 9.3.1. Demographics

For demographic assessment the following parameters will be recorded:

- Year of birth
- Sex
- Race / ethnicity, if allowed per local regulations

### 9.3.2. Medical history

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

- Not pertaining to the study indication
- Start before signature of the IC
- Considered relevant for the subject's study eligibility

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

## 9.4. Efficacy

The primary efficacy endpoint is death or first adjudicated thromboembolic event (DTE) as described under Section 5.3.1. Pertinent information of all clinical events relating to the primary efficacy endpoint or any of its components will be collected between randomization and the visit scheduled after the anticipated efficacy cut-off date is set, and up to 30 days beyond this visit, irrespective of actual treatment of the subject.

Potential efficacy endpoints are adjudicated by the CEC according to the definitions of the CEC charter (see Section 16.1.1).

## 9.5. Pharmacokinetics / pharmacodynamics

Not applicable.

## 9.6. Safety

The primary safety endpoint is primary bleeding event (PBE) as described under Section 5.3.1 Primary variable(s). Pertinent information of all bleeding episodes requiring medical attention will be collected between randomization and the visit scheduled after the anticipated efficacy cut-off date is set, and up to 30 days beyond this visit, irrespective of actual treatment of the subject.

Potential safety endpoints are adjudicated by the CEC according to the definitions of the CEC charter (see Section 16.1.2).

Three bleeding event scales (i.e. BARC, TIMI, and ISTH) are used to classify bleeding events occurring from randomization until the efficacy cut-off date.

### 9.6.1. Adverse events

#### 9.6.1.1. Definitions

**Definition of adverse event (AE)**

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

“Any scheduled surgery that is arranged during the study as a result of a new/deteriorated condition should be reported as (S)AE”, e.g. a new chest pain (SAE) requiring a PCI/CABG (treatment of the SAE).

If laboratory findings reveal abnormal values, if clinically significant, they should be documented and reported as an AE. This is up to the physician’s discretion, and should be documented in the source documentation.

In the following differentiation between medical history and AEs, the term “condition” may include abnormal physical examination findings, symptoms, diseases, laboratory, or ECG findings.

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

**Definition of serious adverse event (SAE)**

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

a. Results in death

b. Is life-threatening

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

c. Requires in-patient hospitalization or prolongation of existing hospitalization

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

   – The admission results in a hospital stay of less than 24 hours

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

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

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

e. Is a congenital anomaly / birth defect

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

### 9.6.1.2. Classifications for adverse event assessment

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

#### 9.6.1.2.1. Seriousness

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

#### 9.6.1.2.2. Intensity

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

- Mild – usually transient in nature and generally not interfering with normal activities
- Moderate – sufficiently discomforting to interfere with normal activities
- Severe – prevents normal activities

#### 9.6.1.2.3. Causal relationship

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

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

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

Possible answers are "yes" or "no"

An assessment of "no" would include:

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

**OR**

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

An assessment of "yes" indicates that the AE is reasonably associated with the use of the study treatment strategy. Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Subject's response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.

- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.
- The assessment is not possible

**Causal relationship to protocol-required procedure(s)**

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

### 9.6.1.2.4. Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

### 9.6.1.2.5. Other specific treatment(s) of adverse events

- None
- Remedial drug therapy

– Other

#### 9.6.1.2.6. Outcome

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

– Recovered/resolved

– Recovering/resolving

– Recovered/resolved with sequelae

– Not recovered/not resolved

– Fatal

– Unknown

### 9.6.1.3. Assessments and documentation of adverse events

The investigator has to record on the respective eCRF pages adverse events as described under Section 9.6.1.1 occurring in the period between the signing of the IC and the end of the follow-up phase; after the end of the clinical follow-up phase there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all serious adverse events (SAEs) the sponsor has to carry out a separate assessment for expectedness, seriousness, and causal relationship to study drug.

### 9.6.1.4. Reporting of SAEs/ AEs

The definition of serious adverse events (SAEs) is given in Section 9.6.1.1.

The following detailed rules apply to AE and SAE handling and are provided in Figure 3 below:

- Primary or secondary efficacy endpoints, including all-cause death, have to be recorded on Efficacy Endpoint pages of the eCRF. Only non-cardiovascular (non-CV) death has to be reported as SAE within 24 hours of the investigator's awareness. All other primary and secondary efficacy endpoints are exempted from expedited reporting.
- All primary and secondary safety endpoints (i.e. bleedings) have to be recorded in the eCRF. Only pericardial bleedings and pulmonary alveolar bleedings/ pulmonary bleedings, which are defined as AEs of special interest (see also Section 9.6.1.6), have to be reported within 24 hours of the investigator's awareness even if classified as non-serious. All other primary and secondary safety endpoints are exempted from expedited reporting.
- All other events (including complications of efficacy or safety endpoints events) that fulfill the seriousness criteria have to be recorded on the AE page of the eCRF and reported within 24 hours of the investigator's awareness.

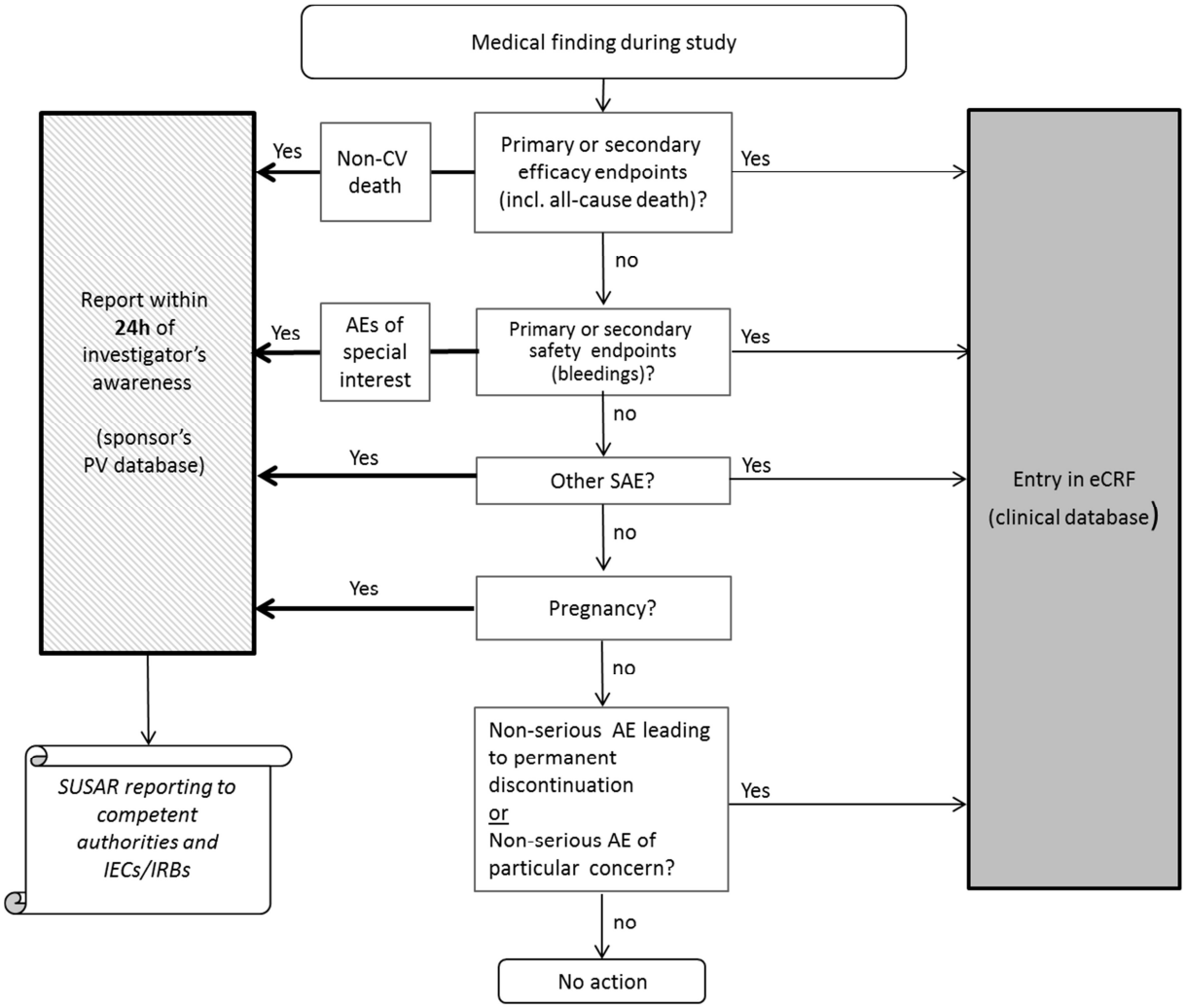
- All pregnancies in female study subjects or in female partner of a male study subject as well as endpoints of the pregnancies have to be reported within 24 hours of the investigator's awareness. For pregnancy reports, the Pregnancy Monitoring Forms are to be used.
- Non-serious AEs that lead to permanent study drug discontinuation have to be recorded on the AE page of the eCRF but do not require further reporting. Non-serious AEs which DO NOT lead to discontinuation of study medication DO NOT NEED to be recorded and reported. However, non-serious AEs that the investigator considers of particular concern may be recorded on the AE page of the eCRF to bring them to the attention of the sponsor.
- Of the AEs reported, reportable events (i.e. SUSARs) have to be reported to the competent authorities and to the Independent IECs/IRBs according to legal requirements.

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

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

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

**Figure 3: Outcome and (S)AE collection and reporting schematic**




## 9.6.1.5. Expected adverse events

For this study, the applicable reference document is the most current version of the investigator's brochure (IB) / summary of product characteristics.

The following events are expected to occur with TAVR and therefore should not be reported as AEs, unless they occur outside of the stated timeframe:

- Back pain related to laying on the procedure table within 3 days after TAVR
- Incisional pain (pain at access site) within 3 days after TAVR
- Sleep problems or insomnia within 7 days after TAVR
- Mild to moderate bruising or ecchymosis within 7 days after TAVR.

#### 9.6.1.6. Adverse events of special safety interest

The following events are considered as AEs of special interest:

- Pericardial bleedings
- Pulmonary alveolar bleedings/pulmonary bleedings

These AEs (even if classified as non-serious) have to be reported within 24 hours of the investigator's awareness by recording them on the AE page of the eCRF.

### 9.6.2. Pregnancies

The reporting of pregnancies is described in Section 9.6.1.4.

### 9.6.3. Further safety

#### 9.6.3.1. Laboratory evaluations

*This section was modified with Amendment 3. For details, see Section 15.2.*

The following local routine laboratory measurements need to be evaluated before randomization:

- Hematology tests
    - Hemoglobin
    - Platelet count
    - White cell count
- Liver tests
    - Transaminases (AST/ALT)
    - Total bilirubin and components (conjugated and/or unconjugated fractions in case of elevated total bilirubin)
    - Alkaline phosphatase, if available as current standard of care
- Renal function
    - Creatinine clearance (CrCl).

      Serum creatinine levels in order to derive the estimated creatinine clearance (mL/min/1.73m$^2$) using the MDRD formula. If serum creatinine levels are not available the estimated creatinine clearance (mL/min/1.73m$^2$) as reported in lab printout should be selected.

Laboratory tests results done as part of standard of care can be used. Hematology tests and renal function results from standard of care can be used as long as collected after the index-TAVR procedure and before randomization. Liver test results collected before TAVR procedure can be used as long as performed as part of the standard of care for the index-TAVR procedure.

For all the laboratory evaluations described above, if multiple values are available, the measurement closest to the visit date should be selected.

#### 9.6.3.2. Physical examination

A targeted physical examination of the cardiovascular and neurological systems will be performed and relevant information will be recorded in the eCRF.

Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

#### 9.6.3.3. 12-lead ECG

Standard 12-lead ECGs will be performed locally as depicted in the schedule of evaluations (Section 9.1) and pertinent information will be recorded in the eCRF. Copies of all recorded ECGs are stored in the patient hospital files.

#### 9.6.3.4. Vital signs

For vital signs the following parameters will be recorded:

- Heart rate
- Blood pressure
- Weight
- Height (only at screening)

### 9.7. Other procedures and variables

**Echocardiography**

Findings from routine echocardiograms (either TTE or TEE) will be collected post-TAVR and at approximately 360 days after randomization (360 ± 90 days or last available between 180-360 days) if available according to the local standard of care for TAVR. Selected hemodynamic parameters will be recorded in the eCRF. Copies of recorded echocardiograms are stored in the patient hospital files.

If an investigational study center is routinely collecting 3D TEE in their post-TAVR subjects, these recordings may be used as the scheduled echocardiograms described above, as long as the sponsor/designated CRO is informed and has approved it accordingly.

### 9.8. Appropriateness of procedures / measurements

The measurements and procedures chosen for this study are widely used, and generally recognized as reliable and accurate.

## 10. Statistical methods and determination of sample size

### 10.1. General considerations

A general description of the statistical methods to be used to analyze the efficacy and safety of the study drug is outlined below. A more detailed statistical analysis plan (SAP) will be provided in a separate document. Statistical analysis will be performed using SAS; the version used will be specified in the SAP. The SAP will accommodate protocol amendments or unexpected issues in study execution or data that affect planned analyses, and will provide

more details on the analytic approaches, coding guidelines, censoring of time-to-event variables, and output tables and figures.

If not stated otherwise, all efficacy and the safety analyses will be based on findings as confirmed by the Clinical Event Committee (CEC). Definitions of terms and endpoints are located in Sections 16.1 and 16.2.

## 10.2. Analysis sets

### 10.2.1. Full analysis set (FAS)

Both the efficacy analysis and the safety analysis are based on the population of all randomized subjects. In accordance with the International Conference on Harmonization (ICH) E9 guidelines, the population of all randomized subjects is termed the Full Analysis Set (FAS).

Subjects are categorized according to the group to which they were assigned by the randomization process.

### 10.2.2. Data scopes

*This section was modified with Amendment 3. For details, see Section 15.2.*

The following data scopes are defined for efficacy and safety analyses.

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

The ITT data scope includes all outcome events observed from randomization until the efficacy cut-off date (i.e. the day of the primary completion event). The follow-up period for each subject will be as long and complete as possible between randomization up to the visit scheduled after the anticipated efficacy cut-off date is set.

**Data scope according to treatment (OT analysis)**

The on-treatment data scope includes all outcome events observed from randomization until two days following permanent discontinuation of the randomized treatment strategy. Subjects are off the rivaroxaban-based treatment strategy when rivaroxaban has been permanently discontinued. Subjects are off the antiplatelet-based treatment strategy when both clopidogrel and ASA have been permanently discontinued within the first 3 months or when ASA alone has been permanently discontinued after 3 months, except in case of NOAF and receiving VKA.

**Data scope until NOAF (pre-NOAF analysis)**

The pre-NOAF data scope includes all outcome events observed from randomization until the NOAF requiring (a switch to) treatment with high dose rivaroxaban or vitamin K antagonists.

**Data scope after NOAF (post-NOAF analysis)**

The post-NOAF data scope includes all outcome events observed between the treatment switch precipitated by NOAF until the efficacy cut-off date.

## 10.3. Variables and planned statistical analyses

### 10.3.1. Primary variables

**Efficacy variables**

The primary efficacy endpoint is the adjudicated composite of all-cause death, any stroke, myocardial infarction (MI), symptomatic valve thrombosis, pulmonary embolism (PE), deep vein thrombosis (DVT), or non-CNS systemic embolism.

**Safety variables**

The primary safety endpoint is defined as the adjudicated composite of life-threatening, disabling or major bleeds classified according to the VARC definitions following the BARC classification. This endpoint is referred to as the primary bleeding event (PBE).

### 10.3.2. Secondary variables

The secondary endpoints are:

- the adjudicated composite of cardiovascular 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).

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

### 10.3.3. Other variables

Other variables include:

- the separate components of the adjudicated primary efficacy and safety endpoint being,
  - 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)
- mean transaortic valve pressure gradient at approximately 360 days after randomization measured by echocardiogram (TTE or TEE)

### 10.3.4. Subgroup variables

*This section was modified with Amendment 3. For details, see Section 15.2.*

The following subgroup variables based on baseline demographics are planned according to the subgroup analysis (see 10.3.8):

- Sex (male, female)
- Age (< Median, ≥ Median)
- Weight
- BMI
- Valve type (balloon-expandable, self-expandable)
- Valve-in-valve procedure
- Surgical Risk Scores, such as Society of Thoracic Surgeons' (STS) risk score and/or EuroSCORE
- Renal function
- 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)
- $CHADS_2$ and $CHA_2DS_2$-VASc scores (< Median, ≥ Median)
- HAS-BLED (< Median, ≥ Median)
- Frailty index

### 10.3.5. Analysis of the primary efficacy variable

*This section was modified with Amendment 3. For details, see Section 15.2.*

The analysis of the primary efficacy variable is performed on the Full Analysis Set (FAS). For superiority analysis the follow-up is censored at the last date of known outcome status or at the efficacy cut-off date, whichever comes first. Non-inferiority analysis is carried out under the OT data scope, i.e. follow-up is censored at two days after permanent discontinuation of the randomized treatment strategy. Censoring is assumed independent of the treatment group assignment.

### 10.3.5.1. Testing for superiority

*This section was modified with Amendment 3. For details, see Section 15.2.*

In order to evaluate whether the rivaroxaban-based strategy is superior to the antiplatelet-based strategy in prolonging the time to primary efficacy outcome event in patients with post-TAVR patients, the following null hypothesis ($H_0$) is tested 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 outcome for all time points")

The one-sided alternative hypothesis 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 a difference between the two groups in favor of the rivaroxaban-based treatment group regarding the primary efficacy outcome for at least one time point")

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 estimates of cumulative risk and cumulative hazard functions 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.

Hazard ratio and corresponding two-sided 95% confidence intervals are estimated based on a Cox proportional hazards models. The parameter estimate $\beta$ (=ln(HR)), its standard error, p-value, and 95% Confidence Limits are calculated according to the maximum partial likelihood method, with Breslow's approximation for ties (phreg).

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

All of the above analyses are carried out under the ITT data scope (i.e. all events are counted irrespective of the actual treatment at the time of the event).

Further details will be specified in SAP.

### 10.3.5.2. Testing for non-inferiority

*This section was modified with Amendment 3. For details, see Section 15.2.*

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

> $H_0$: HR(t) ≥ 1.2 for all time points t ≥ 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:

> $H_1$: HR(t) < 1.2 for all time points t ≥ 0, (i.e. "the hazard in the rivaroxaban-based treatment group for the primary efficacy endpoint is such that the HR is below 1.20")

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

> If the upper boundary of 95% confidence interval (CI) for HR falls below 1.20, 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.

Hazard ratio and corresponding two-sided 95% confidence intervals are estimated based on a Cox proportional hazards model.

In order to preserve the type I error rate for efficacy testing, the two tests for the primary efficacy endpoint are technically placed in a hierarchical order, (1) testing for non-inferiority as described in this section followed by (2) testing for superiority as described in the previous section.

### 10.3.5.3. Exploratory analyses of the primary efficacy variable

In the primary analyses, switches to full dose anticoagulation are treated as integral part of the treatment strategy. Pre-NOAF analyses, with censoring at the time of the switch to anticoagulation therapy, are carried out as exploratory analyses. Post-NOAF analyses, with starting at the time of the treatment switch precipitated by NOAF are carried out as exploratory analyses.

## 10.3.6. Analysis of secondary and other efficacy variables

The secondary efficacy and net-benefit variables are tested sequentially in a hierarchical order as listed in Section 10.3.2.

If the superiority of rivaroxaban-based strategy for the primary efficacy outcome is declared, the following alternative hypotheses, superiority of rivaroxaban-based strategy compared with antiplatelet-based strategy for the secondary efficacy endpoints is tested in the sequential order. 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 controls the global Type 1 error level.

The analysis methods are similar to those described for the primary efficacy variable. The analyses are carried out under the ITT data scope. In these analyses, testing for superiority is not preceded by testing for non-inferiority.

### 10.3.7. Analysis of the safety variables

*This section was modified with Amendment 3. For details, see Section 15.2.*

The analysis of the primary safety variable is performed on the Full Analysis Set (FAS) under the ITT data scope — that is, events are analyzed irrespective of their time of occurrence relative to termination of assigned study treatment strategy. Follow-up is censored at the last date of known outcome status or at the efficacy cut-off date, whichever comes first.

Kaplan-Meier estimates of cumulative risk and cumulative hazard functions for the primary safety variable 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.

If the proportional hazards assumption holds for the primary safety variable, hazard ratio and corresponding two-sided 95% confidence intervals are estimated based on a Cox proportional hazards models.

On treatment analyses, pre-NOAF and post-NOAF analyses of the primary safety variable are performed as exploratory analyses.

All of the above analyses of the primary safety variable are descriptive, without formal statistical tests being performed.

The analyses of secondary safety variables are similar to those for secondary efficacy variables, without any sequential order.

### 10.3.8. Subgroup analysis

Subgroup analyses for the primary efficacy and safety variables are based on the same analysis sets and data scopes as in the main analyses of the study outcome variables. 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. Additionally the hazard ratio for the treatment effect is 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 variables will be interpreted as “flags” to prompt further investigation. This further investigation includes the likelihood ratio test proposed by Gail and Simon to test for qualitative interaction.

## 10.4. Determination of sample size

*This section was modified with Amendment 3. For details, see Section 15.2.*

The sample size determination for the study was driven by requirements for testing superiority of the rivaroxaban-based strategy over the antiplatelet-based strategy as described above.

The expected 540 days event rate of the primary efficacy endpoint is 33.0% (5-7, 10). The target Relative Risk at 540 days is 0.80, i.e. a reduction of the 540 days event rate from 33.0% under antiplatelet-based regimen to 26.4% under the rivaroxaban-based regimen. Under the assumption of an exponential distribution, the hazard ratio equals 0.7654.

Under the above assumptions, with 360 days accrual period, and an 540 days median follow-up (minimum 360 days and maximum 720 days), randomization of 2 x 740 analyzable subjects is expected to yield 440 primary events (196 in the rivaroxaban-based treatment group and 244 in the antiplatelet-based control group). This provides 80% power at a 5% significance level, without interim analyses for efficacy.

The power calculation was based on a test using the Cox proportional hazards model and was performed with PASS version 12.0.6, with the module for two survival curves using Cox's proportional hazards model.

A sample size of sample size of 2 x 760 subjects allows for an attrition rate of 2.63%. The study is event driven and the number of randomized subjects is estimated to be required to collect 440 primary efficacy events. The study is planned to run until this number of events has been reached or to stop earlier if the event rate is unexpectedly low.

With this sample size, the study has > 90% power to show non-inferiority with a non-inferiority margin of 1.20 if the underlying hazard ratio ≤ 0.90 at a one-sided significance level of 2.5%. The non-inferiority margin of 1.20 was selected based on clinical appropriateness.

The final sample size will depend on multiple factors including the rate of accrual of the primary endpoint events. The Steering Committee of the trial will monitor the aggregate (blinded) event rate and may increase the sample size or duration of follow-up to achieve the planned target number of events in consultation with the sponsor.

**Non-inferiority margin**

The non-inferiority margin of 1.20 for the HR for the efficacy comparison as described in Section 10.3.5.2 was selected based on both clinical appropriateness and relevant studies in the area of TAVR.

The event rates for mortality and ischemic events after TAVR are high. In high-risk subjects receiving TAVR in the PARTNER trial the composite of the rate of all-cause death or stroke was at 27% and 37% in the TAVR group after 1 and 2 years, respectively (14). The standard of care antithrombotic treatment after TAVR is dual antiplatelet therapy followed by single antiplatelet therapy with ASA although evidence from randomized control trials (RCTs) is lacking. Moreover, no prospective randomized studies to date have compared an active to no antithrombotic treatment in subjects after TAVR.

Earlier studies comparing TAVR with SAVR used a non-inferiority margin of 1.23 for RR of one year all-cause mortality (5, 10, 61).

In addition, NOAF is observed in up to 30% of subjects undergoing TAVR and has been demonstrated as single, independent predictor of stroke during the subacute phase after TAVR (13). Rivaroxaban has been approved for stroke prevention in non-valvular AF based on the positive results from the ROCKET AF trial (52), investigating rivaroxaban compared to VKA. In ROCKET AF a NI margin of 1.46 was applied but for a much lower event rate (2.2% per 100 patient years) than the one expected post-TAVR.

Taking into consideration both the historical NI margins used in TAVR trials together with the expected high event rates and the considerable proportion of subjects with NOAF after randomization, a non-inferiority margin of 1.20 was chosen for this study.

### 10.5. Planned interim analyses

*This section was modified with Amendment 3. For details, see Section 15.2.*

No formal interim analysis is planned.

## 11. Data handling and quality assurance

### 11.1. Data recording

*This section was modified with Amendment 3. For details, see Section 15.2.*

The data collection tool for this study is a validated electronic data capture system called MARVIN (XClinical).

Data required according to this protocol are recorded by investigational site personnel via data entry into the internet based eCRF system, which Cardialysis (CRO) licenses from XClinical. MARVIN is validated by XClinical and Cardialysis for use in its clinical studies. MARVIN allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Cardialysis extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by XClinical and will be downloaded by Cardialysis each night. All access to the MARVIN system is through a password-protected security system that is part of the MARVIN software.

All internal Cardialysis, internal Mount Sinai (ARO), Bayer, and external investigator site personnel seeking access must go through a MARVIN training process before they are granted access to MARVIN for use in Bayer's clinical studies. Training records are maintained.

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

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

**Source documentation**

It is the expectation of the sponsor that key data entered into the eCRF has source documentation available at the site.

Study-specific data not needed for the subject's routine medical care (e.g. scores or questionnaires) may be entered directly into the eCRF, without availability of corresponding source documentation.

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

**Data recorded from screening failures**

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

- Demographic information (SID number; year of birth / age; sex; if applicable race / ethnicity)
- Date of IC
- Reason for failure of screening
- Date of last visit

If a subject is deemed a screening failure, all SAEs experienced during the screening period are documented and reported as described in Section 9.6.1.4 and 9.6.1.6.

## 11.2. Monitoring

*This section was modified with Amendment 3. For details, see Section 15.2.*

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

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

- Data are authentic, accurate, and complete
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes)

- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met

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

## 11.3. Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. IxRS, laboratory, ECG, adjudication committees).

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

## 11.4. Missing data

Every effort will be undertaken to enhance completeness of data.

In time-to-event analysis subjects who have intentionally terminated follow-up will be censored at the time of the efficacy cut-off date. If loss-to-follow-up occurs, follow-up will be censored at the last date of known clinical outcome status.

Unless otherwise specified in the statistical analysis plan, no statistical techniques will be used to impute missing data for continuous or categorical variables. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

## 11.5. Audit and inspection

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

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

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

### 11.6. Archiving

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

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

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

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

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

## 12. Premature termination of the study

*This section was modified with Amendment 3. For details, see Section 15.2.*

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If benefit-risk ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)

    The DSMB will have the responsibility for recommending early termination of the study to the Steering Committee and the sponsor, which will have ultimate authority/responsibility for making the decision. The criteria that the DSMB will follow to determine whether/when to recommend termination of the study will be detailed in DSMB charter (separate document).
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.

- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing subjects, including those in any post-study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal from the study can be found in Section 6.3 .

# 13. Ethical and legal aspects

## 13.1. Investigator(s) and other study personnel

### 13.1.1. Committees

A Steering Committee will have overall responsibility for the conduct and reporting of the study as defined under the Steering Committee Charter. This committee will meet as needed.

An independent Data Safety Monitoring Board (DSMB) will be commissioned for this study. This committee will monitor the progress of the study and ensure that the safety of subjects is not compromised. Any recommendations from the DSMB will be made available to the Steering Committee.

An independent Clinical Endpoint Committee (CEC) blinded to treatment allocation will apply the protocol definitions and adjudicate and classify the defined efficacy and safety endpoints. These adjudicated endpoints will form the basis for the final study analyses.

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

The protocol allows performance of “local” ancillary studies aimed at investigating underlying mechanisms of action. Ancillary studies will be fully documented in separate protocol annexes and must be approved by the Steering Committee and its local IRB/IEC.

### 13.1.2. Other study personnel

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

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

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

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

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

## 13.2. Funding and financial disclosure

### Funding

This study will be funded by its sponsor.

### Financial disclosure

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

## 13.3. Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

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

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

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

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

## 13.4. Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and IC form provided by the sponsor or the study center. The sample of subject information sheet and IC form is provided as a document separate to this protocol.

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

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

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

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers post-treatment period examinations as specified in the visit description described in Section 9.1 and 9.2.2 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The subject has the right to object to the generation and processing of this post-withdrawal data. For this, he/she needs to sign a corresponding declaration of objection; alternatively, the subject's oral objection may be documented in the subject's source data.

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

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

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

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

If allowed by subject, his/her General Practitioner (GP) will be informed of the subject's participation in the trial by means of a letter from the investigator (included in the subject information sheet package). Information will be included on the treatment strategies as well as on specific clinical assessments that must come to the attention of the study center before subject's treatment is modified (such as, NOAF is detected).The IC form and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to

the protocol that requires a change to the content of the subject information and / or the written IC form. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised IC form. Any revised written IC form and written information must receive the IEC/ IRB`s approval / favorable opinion in advance of use.

## 13.5. Publication policy and use of data

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

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

## 13.6. Compensation for health damage of subjects / insurance

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

## 13.7. Confidentiality

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

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the IC process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject’s identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

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# 15. Protocol amendments

## 15.1. Amendment 1

Amendment 1 is dated 28 SEP 2015.

### 15.1.1. Overview of changes

#### 15.1.1.1. Modification 1: IMP/NIMP terms removed from protocol

Reference to investigational and non-investigational medicinal products (IMP and NIMP) was removed because of different local requirements in the participating countries.

Sections affected by this modification:

- Synopsis
- Section 7.1 Treatments to be administered
- Section 7.2 Identity of study treatment
- Section 7.2.1 Rivaroxaban
- Section 7.2.2 Clopidogrel, ASA and VKA

#### 15.1.1.2. Modification 2: Clarification on supply of standard-of-care drugs

A sentence was added clarifying the supply and labeling of clopidogrel, ASA and VKA.

Section affected by this modification: Section 7.2.2 Clopidogrel, ASA and VKA.

### 15.1.2. Changes to the protocol text

#### 15.1.2.1. Synopsis

This section was changed as a result of Modification 1.

*Deleted text:*

| | |
|---|---|
| **Dose(s)** | [...] ~~In this strategy, rivaroxaban is considered the investigational medicinal product (IMP) and ASA is considered as a non-investigational medicinal product (NIMP).~~ |

*Deleted text:*

| | |
|---|---|
| **Dose(s)** | [...] ~~In this strategy clopidogrel, ASA and VKA are considered as a NIMP.~~ |

### 15.1.2.2. Section 7.1 Treatments to be administered

This section was changed as a result of Modification 1.

*Old text:*

Study treatment assignment will be open-label. Study treatments consist of ~~the IMP (~~rivaroxaban~~)~~ and in addition of ~~the NIMPs (~~clopidogrel, ASA, VKA~~)~~ which are systematically prescribed to TAVR subjects in accordance to the relevant guidelines (8, 30, 33).

*New text*:

Study treatment assignment will be open-label. Study treatments consist of rivaroxaban and in addition of the standard of care treatments clopidogrel, ASA, and VKA, which are systematically prescribed to TAVR subjects in accordance to the relevant guidelines and routine clinical practice (8, 30, 33).

### 15.1.2.3. Section 7.2 Identity of study treatment

This section was changed as a result of Modification 1.

*Old text*:

Rivaroxaban ~~is the investigational medicinal product (IMP) and as such~~ will be labeled according to the requirements of local law and legislation.

*New text:*

Rivaroxaban will be labeled according to the requirements of local law and legislation.

### 15.1.2.4. Section 7.2.1 Rivaroxaban

This section was changed as a result of Modification 1.

*Old text:*

Tablets are for oral use. Rivaroxaban is part of the rivaroxaban-based treatment strategy ~~and also the study's investigational medicinal product (IMP)~~.

*New text:*

Tablets are for oral use. Rivaroxaban is part of the rivaroxaban-based treatment strategy.

### 15.1.2.5. Section 7.2.2 Clopidogrel, ASA and VKA

This section was changed as a result of Modifications 1 and 2.

*Old text:*

Clopidogrel, ASA~~,~~ and VKA ~~are NIMPs and as such~~ will be supplied from local investigative centers' resources and will be used according to the product labeling for the approved formulations.

*New text:*

Clopidogrel, ASA and VKA will be supplied from local investigative centers' resources and will be used according to the product labeling for the approved formulations. If required by

local regulations, Bayer will purchase these drugs from local commercial sources, and label and distribute to the investigational site.

## 15.2. Amendment 3

### 15.2.1. Overview of changes

#### 15.2.1.1. Modification 1: Clarify the timing of the first dose of rivaroxaban

Clarification was made when to start rivaroxaban for the subjects who are not on clopidogrel (ie, at the time of randomization). The timing of the start of rivaroxaban for the subjects who are on clopidogrel was changed from 24-72 hours to 1 to 3 days because of logistical concerns regarding the counting of hours. Timing in relation to TAVR was added in case the start of the study medication is on the next day after TAVR.

Sections affected by this modification:

- Synopsis
- Section 5.2 Study plan
- Section 7.1.1 Rivaroxaban-based strategy (experimental strategy)

#### 15.2.1.2. Modification 2: Revision of TAVR inclusion criterion

Subjects eligible for inclusion are those with successful TAVR of a native aortic valve stenosis with any approved/marketed device. This has been revised to also include valve-in-valve replacements. The word native is deleted to allow inclusion of subjects with previous TAVR device implanted or subjects with a surgical aortic valve replacement with a non-metallic valve device. Non native aortic stenosis subjects that undergo a novel successful TAVR procedure and may also benefit to receive a rivaroxaban based strategy.

Clarifications were also made to the definition of a successful TAVR. The peak transvalvular velocity requirement was reworded to be consistent with the eCRF. Text was added to clarify that successful TAVR includes the absence of any type of periprocedural stroke as hemorrhagic stroke and ischemic stroke are both clearly addressed in specific exclusion criteria.

Sections affected by this modification:

- Synopsis
- Section 5.2 Study plan
- Section 6.1 Inclusion criteria

#### 15.2.1.3. Modification 3: Clarification to the DAPT exclusion criteria

The exclusion criterion was revised because it was not clear to the sites that patients with indication of DAPT cannot be randomized because DAPT cannot be kept in rivaroxaban-based strategy. The new text clarifies that if the patient has a recommendation of ongoing use of DAPT at the time of screening, the patient is not eligible for GALILEO, because the

patient has a 50% chance to be randomized to rivaroxaban-based strategy, which does not allow the concomitant use of DAPT.

Sections affected by this modification:

- Synopsis
- Section 6.2 Exclusion criteria

#### 15.2.1.4. Modification 4: Timing of assessments

The timing of randomization has been changed from 2-7 days after a successful TAVR to 1-7 days after the procedure. Recent data published regarding TAVR being an option for intermediate risk patients leads to a broader indication of TAVR and patients with lower risk are discharged from the hospital earlier. This change reflects current clinical practice. "Calendar" was removed when specifying days.

Text was modified for consistency to specify that the screening is 1-7 days post-TAVR rather than 1-7 days prior to randomization.

In addition, "Study Day 0" (ie, baseline/randomization) has been deleted because it was confusing to the sites.

Clarification was added to specify the timing of visits is from randomization.

Other minor clarifications were made.

Sections affected by this modification:

- Synopsis
- Section 5.1 Study flow diagram
- Section 5.2 Study plan
- Section 9.1 Tabular schedule of evaluations
- Section 9.2.1 Screening period (screening and randomization)
- Section 9.2.2 Planned treatment period

#### 15.2.1.5. Modification 5: Update the list of abbreviations

Effective in 2015, the International Conference on Harmonization is now known as the International Council for Harmonization.

Section affected by this modification:

- List of abbreviations

#### 15.2.1.6. Modification 6: Allowance of subjects with history of prostate cancer to participate

The criterion excluding subjects from the study with active malignancies has been revised to allow subjects with non-active prostate cancer to participate in the study. Due to the elderly population expected in this study, it is anticipated that some subjects will have a history of prostate cancer.

Section affected by this modification:

- Section 6.2 Exclusion criteria

### 15.2.1.7. Modification 7: Clarification made to the recording and use of prior and concomitant medications

Clarification was made which medications should be recorded in the eCRF, including medications used prior and during TAVR. Also, for some of the disallowed therapies, specification was added as to which study treatment strategy they apply to.

Section affected by this modification:

- Section 8.1 Prior and concomitant therapy

### 15.2.1.8. Modification 8: Text added to visit 1 – baseline / randomization

For the 12-lead ECG required at Visit 1, the underlined text was added: "12-lead electrocardiogram (ECG) or any other method documenting heart rhythm (e.g. ECG strip) able to exclude atrial fibrillation" to guarantee that atrial fibrillation is excluded by the time of randomization, in case the 12-lead ECG was not performed close to randomization.

Section affected by this modification:

- Section 9.2.1 Screening period (screening and randomization)

### 15.2.1.9. Modification 9: An end of study visit has been added

An end of study visit has been added, which will be done once the 440 outcomes are reached. This visit will be performed for subjects who early permanently discontinue the study medication and had the expectation to keep the regular scheduled visits as planned by the time of study drug discontinuation. This visit will also be performed for subjects who withdraw consent and allow collection of further information.

GALILEO is an event-driven study and the statistical analysis is based in the intention-to-treat (ITT) principle. ITT analysis includes every subject who is randomized according to randomized treatment assignment. A better application of the ITT approach is possible if complete outcome data are available for all randomized subjects. That is why it is so important to guarantee that all randomized patients, regardless of the study drug intake, are assessed by the end of study at least regarding safety/efficacy outcomes and SAEs/AE of special interest, especially those subjects that early permanent discontinue the study drug. Therefore, the addition of an end of study visit has the purpose to minimize missing data regarding safety and efficacy events and guarantee that high quality data are delivered as the analysis set will be based in the ITT approach.

Sections affected by this modification:

- Section 9.1 Tabular schedule of evaluations
- Section 9.2.3 Post-treatment period

### 15.2.1.10. Modification 10: Laboratory testing at screening

Specification was added that the testing of total bilirubin and its components will be performed in the case of elevated total bilirubin, because the evaluation of conjugated and/or unconjugated fractions when total bilirubin is within normal range is not clinically significant. Laboratory test results evaluated during screening can derive from the standard of care.

A provision was added to allow the use of liver test results collected before TAVR procedure as long as performed as part of the standard of care for the index-TAVR procedure. This change aims to clarify the time window of the collection of the test as standard of care before and after TAVR procedure.

Specification was added that laboratory tests that are performed as part of routine medical practice are acceptable as long as they are done after the TAVR procedure and before randomization. A sentence was deleted specifying that all clinical laboratory results performed during screening are used to confirm eligibility for randomization, as some of the liver function tests are not directly used to confirm eligibility. Clarification as to the time of the measurements was made.

Sections affected by this modification:

- Section 9.1 Tabular schedule of evaluations
- Section 9.2.1 Screening period (screening and randomization)
- Section 9.6.3.1 Laboratory evaluations

### 15.2.1.11. Modification 11: Purpose of physical examination added

Wording was added to clarify that the purpose of the physical examinations is to investigate any occurrence of a safety or efficacy outcome.

Section affected by this modification:

- Section 9.1 Tabular schedule of evaluations

### 15.2.1.12. Modification 12: Revision of statistical methods

To the stopping criterion (reaching 440 efficacy events) “or earlier if the event rate is unexpectedly low” was added.

Rationale: To enable regular ending of the study in case the rate of efficacy outcomes is much lower than expected and the time to reach 440 events would be estimated markedly later than beginning of 2018. For a reasonable time point to stop the study the observed overall event rate and the overall time at risk (of all patients) will be considered. The treatment effect will be assumed to be as in the planning assumption (see determination of sample size). It was also considered that the prolongation of the FU time may lead to a dilution of the treatment effect, especially in case of study drug discontinuation and treatment switch.

Statistical method was changed to test for superiority of the primary efficacy endpoint using log-rank test.

Rationale: updated text has been implemented to comply with this Bayer standard, which is to be used for one-sided superiority tests in time-to-event analyses.

The text "with the Cox proportional hazard model" was deleted. Reason: Cox proportional hazard model described in the synopsis can lead to misleading interpretation of how the primary endpoints will be evaluated regarding the changes in the statistical session in this protocol amendment.

The text "the primary safety endpoint (PBE) is tested for non-inferiority with a hazard ratio NI margin at 1.50 using the ITT approach" was deleted. Rationale: In response of the FDA advise letter, it was committed to remove the non-inferiority margin for the primary safety endpoint, as it was agreed that rate of acceptable bleeding is dependent on the magnitude of treatment benefit (if any) and the treatment benefit will not be known until the study is concluded and analyzed.

The text "therefore, the sample size may be increased if planning assumptions are modified based on blinded data review." was deleted. Rationale: as there will be no formal interim analysis, the deleted text is obsolete.

Data scope after NOAF (post-NOAF analysis): The text "i.e. EOT visit performed" was deleted.

Rationale: The deletion of this sentence was required because it may not be applicable for subjects that early permanently discontinued study drug and will require an end of study visit (added in this protocol amendment).

Power analysis for safety was deleted. Rationale: As per FDA letter of advice, there are no useful data for establishing an NI margin for primary safety endpoint.

Sections affected by this modification:

- Synopsis
- Section 4.1 Primary objective(s)
- Section 5.1 Study flow diagram
- Section 5.3.3 Other variable(s)
- Section 9.1 Tabular schedule of evaluations
- Section 9.2.2 Planned treatment period
- Section 10 Statistical methods and determination of sample size

### 15.2.1.13. Modification 13: Exclusion of planned interim analysis

The interim analysis has been removed. An interim analysis after day 270 of the last patient does not seem feasible/meaningful any more with the new recruitment plan. The study may even end earlier.

An interim analysis after 300 events may be only 3-4 month before the regular study end and not much can be gained by stopping early.

The interim analysis would not affect recruitment. And an early termination of the study seems only desirable in case of a negative risk-benefit assessment. In that case the DSMB can intervene at any time.

Sections affected by this modification:

- Section 10.5 Planned interim analyses
- Section 12 Premature termination of the study

#### 15.2.1.14. Modification 14: Minor editorial/consistency/clarification/ administrative changes

Sections affected by this modification:

- Signature of the sponsor's medically responsible person
- Section 7.6 Drug logistics and accountability
- Section 9.1 Tabular schedule of evaluations
- Section 9.2.1 Screening period (screening and randomization)
- Section 16.2 Definition of terms

#### 15.2.1.15. Modification 15: Text updated to account for local legal requirements

Subjects' general practitioners will be notified of their participation in the trial if required by local legal requirements.

Section affected by this modification:

- Section 9.2.1 Screening period (screening and randomization)

#### 15.2.1.16. Modification 16: CRO and ARO specification

Specification has been added to clarify that Cardialysis is the CRO for the study and Mount Sinai is the ARO for the study.

Sections affected by this modification:

- List of abbreviations
- Section 7.6 Drug logistics and accountability
- Section 11.1 Data recording
- Section 11.2 Monitoring

### 15.2.2. Changes to the protocol text

In this section, all sections affected by the amendment are shown in sequence following the previous protocol version. Administrative, and minor editorial and formatting changes are not shown. Deletions to the protocol text are ~~crossed out~~; additions are <u>underlined</u>.

### 15.2.2.1. Signature of sponsor's medically responsible person

This section was changed as a result of Modification 14.

*Old text:*

Name: PPD Role: PPD

*New text:*

Name: PPD Role: PPD

### 15.2.2.2. Synopsis

This section was changed as a result of Modifications 1, 2, 3, 4, and 12.

*Old text:*

| | |
|---|---|
| **Study objective(s)** | 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).<br>To assess ~~whether a~~ rivaroxaban-based strategy, following TAVR, compared to an antiplatelet-based strategy, ~~is non-inferior towards primary bleeding events (PBE).~~ |

*New text:*

| | |
|---|---|
| **Study objective(s)** | 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).<br>To assess the primary bleeding events (PBE) of the rivaroxaban-based strategy, following TAVR, compared to an antiplatelet-based strategy. |

*Old text:*

| | |
|---|---|
| **Duration of treatment** | The first dose of rivaroxaban (10 mg once-daily) is ~~given either immediately after~~ ~~randomization~~ or within ~~24-72 hours~~ after the last intake of clopidogrel. Rivaroxaban 10 mg once-daily can be taken with or without food. ASA 75-100 mg once-daily is to be continued unchanged or started immediately after randomization if not already being taken. ASA is discontinued after 90 days from randomization. Rivaroxaban is continued until the efficacy cut-off date, i.e. when the predefined number of efficacy endpoints is reached. In the event of NOAF the dose of rivaroxaban is switched from 10 mg once-daily to 20 or 15 mg once-daily, depending on renal function. Rivaroxaban 20 and 15 mg once-daily should be taken with food. Up to 90 days after randomization, ASA 75-100 mg once-daily is to be continued unchanged. After 90 days from randomization, ASA is discontinued and rivaroxaban 20 or 15 mg once-daily is continued alone until the efficacy cut-off date. |

*New text:*

| | |
|---|---|
| **Duration of treatment** | The first dose of rivaroxaban (10 mg once-daily) is started at the time of randomization if the subject is not on clopidogrel or within 1-3 days after the last intake of clopidogrel. In case study medication is started the next day post-TAVR, study medication should not be started earlier than the time the TAVR was done on the previous day and the subject should be stabilized and complication or bleedings should have been excluded carefully. Rivaroxaban 10 mg once-daily can be taken with or without food. ASA 75-100 mg once-daily is to be continued unchanged or started immediately after randomization if not already being taken. ASA is discontinued after 90 days from randomization. Rivaroxaban is continued until the efficacy cut-off date, i.e. when the predefined number of efficacy endpoints is reached or earlier if the event rate is unexpectedly low. In the event of NOAF the dose of rivaroxaban is switched from 10 mg once-daily to 20 or 15 mg once-daily, depending on renal function. Rivaroxaban 20 and 15 mg once-daily should be taken with food. Up to 90 days after randomization, ASA 75-100 mg once-daily is to be continued unchanged. After 90 days from randomization, ASA is discontinued and rivaroxaban 20 or 15 mg once-daily is continued alone until the efficacy cut-off date. |

*Old text:*

| | |
|---|---|
| **Diagnosis and main criteria for inclusion /exclusion** | Key inclusion criteria:<br>• Successful TAVR of ~~a native~~ aortic valve stenosis |

| | |
|---|---|
| | ….<br>Key exclusion criteria:<br>….<br>• Any indication for dual-antiplatelet therapy (DAPT) ~~for more than 3 months after randomization (such as coronary, carotid or peripheral stent implantation)~~<br>….<br>Screening, IC and randomization:<br>Subjects are screened for inclusion after TAVR. Consenting subjects must be randomized within ~~2~~ 7 days after a successful TAVR and before hospital discharge. |

*New text:*

| | |
|---|---|
| **Diagnosis and main criteria for inclusion /exclusion** | Key inclusion criteria:<br>• Successful TAVR of an aortic valve stenosis (either native or valve-in-valve)<br>….<br>Key exclusion criteria:<br>….<br>• Any ongoing absolute indication for dual antiplatelet therapy (DAPT) at time of screening that is unrelated to the TAVR procedure<br>….<br>Screening, IC and randomization:<br>Subjects are screened for inclusion after TAVR. Consenting subjects must be randomized within 1-7 days after a successful TAVR and before hospital discharge. |

*Old text:*

| | |
|---|---|
| **Methodology** | The primary comparison will be to test the superiority of a rivaroxaban-based strategy to an antiplatelet-based strategy with respect to the primary efficacy endpoint. This comparison is preceded by a non-inferiority test that must be satisfied.<br>~~Further, non-inferiority of a rivaroxaban-based strategy to an antiplatelet-based strategy towards the primary safety endpoint will be tested.~~ |

*New text:*

| | |
|---|---|
| **Methodology** | The primary comparison will be to test the superiority of a rivaroxaban-based strategy to an antiplatelet-based strategy with respect to the primary efficacy endpoint. This comparison is preceded by a non-inferiority test that must be satisfied.<br><br>Estimates of the hazard ratio for bleeding events together with their 95% confidence intervals will be calculated for descriptive purposes. |

*Added text:*

| | |
|---|---|
| **Time point/frame of measurement for primary variable(s)** | Subjects are treated and followed from randomization until the study ends, i.e. when the predefined number of primary efficacy endpoints is reached or earlier if the event rate is unexpectedly low and study closure activities are completed. Therefore, the duration of the treatment period for a given subject will depend on the time required to collect these events. The expected duration of the study is 750 days, but depending upon the rate of subject recruitment and endpoint event rates it may be adapted. Regular assessments are planned to take place during the study. |

*Old text:*

| | |
|---|---|
| **Plan for statistical analysis** | The primary endpoints (for efficacy and for safety) are analyzed as a time-to-event endpoint ~~with the Cox proportional hazard model~~, in the full analysis set (FAS) of all randomized subjects.<br><br>The primary efficacy endpoint (DTE) is tested for superiority. This test is preceded by a non-inferiority (NI) test with a hazard ratio NI margin at 1.20 using the on-treatment approach. If non-inferiority is met, a test for superiority is performed using the intention-to-treat (ITT) approach. ~~The primary safety endpoint (PBE) is tested for non-inferiority with a hazard ratio NI margin at 1.50 using the ITT approach.~~ |

*New text:*

| | |
|---|---|
| **Plan for statistical analysis** | The primary endpoints (for efficacy and for safety) are analyzed as a time-to-event endpoint, in the full analysis set (FAS) of all randomized subjects.<br><br>The primary efficacy endpoint (DTE) is tested for superiority using log-rank test. This test is preceded by a non-inferiority (NI) test with a hazard ratio NI margin at 1.20 using the on-treatment approach. If non-inferiority is met, a test for superiority is performed using the intention-to-treat (ITT) approach. |

### 15.2.2.3. List of abbreviations

This section was changed as a result of Modifications 5 and 16.

*Old text:*

| | |
|---|---|
| ICH | International ~~conference on~~ harmonization |

*New text*:

| | |
|---|---|
| ARO | Academic research organization |
| ICH | International Council for Harmonization |

### 15.2.2.4. Section 4.1 Primary objective(s)

This section was changed as a result of Modification 12.

*Old text:*

….

~~To assess whether a rivaroxaban-based strategy, following TAVR, compared to an antiplatelet-based strategy, is non-inferior towards primary bleeding events (PBE).~~ 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.

*New text:*

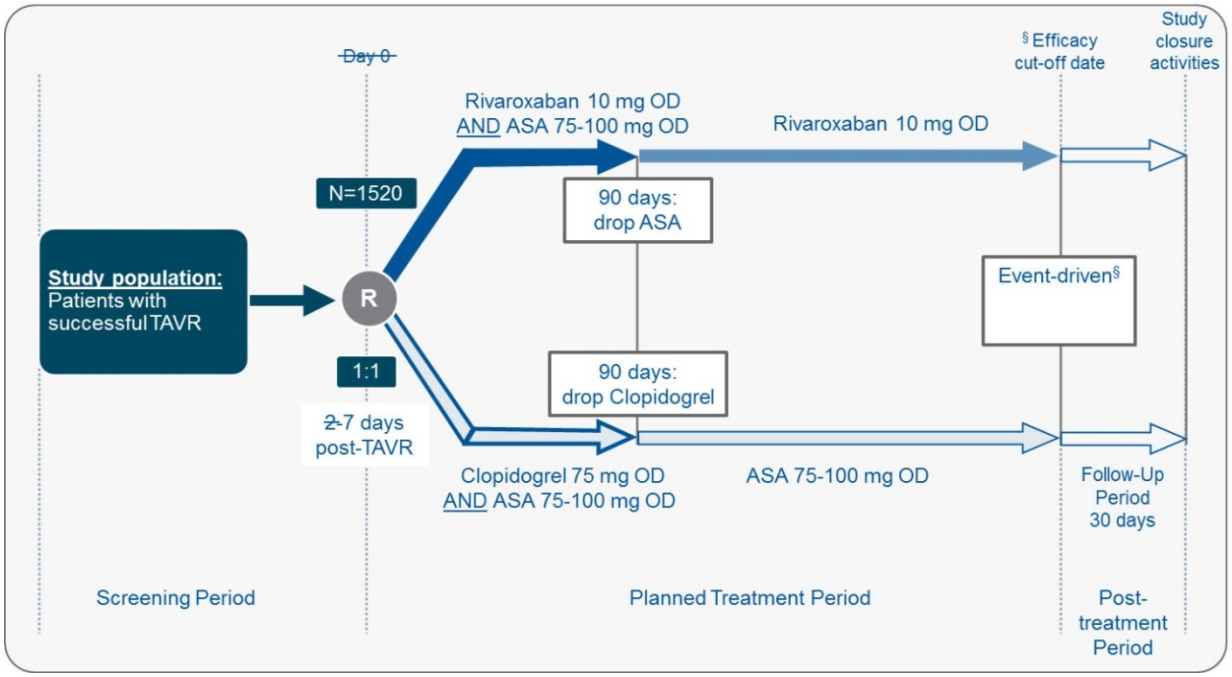
….

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.

### 15.2.2.5. Section 5.1 Study flow diagram

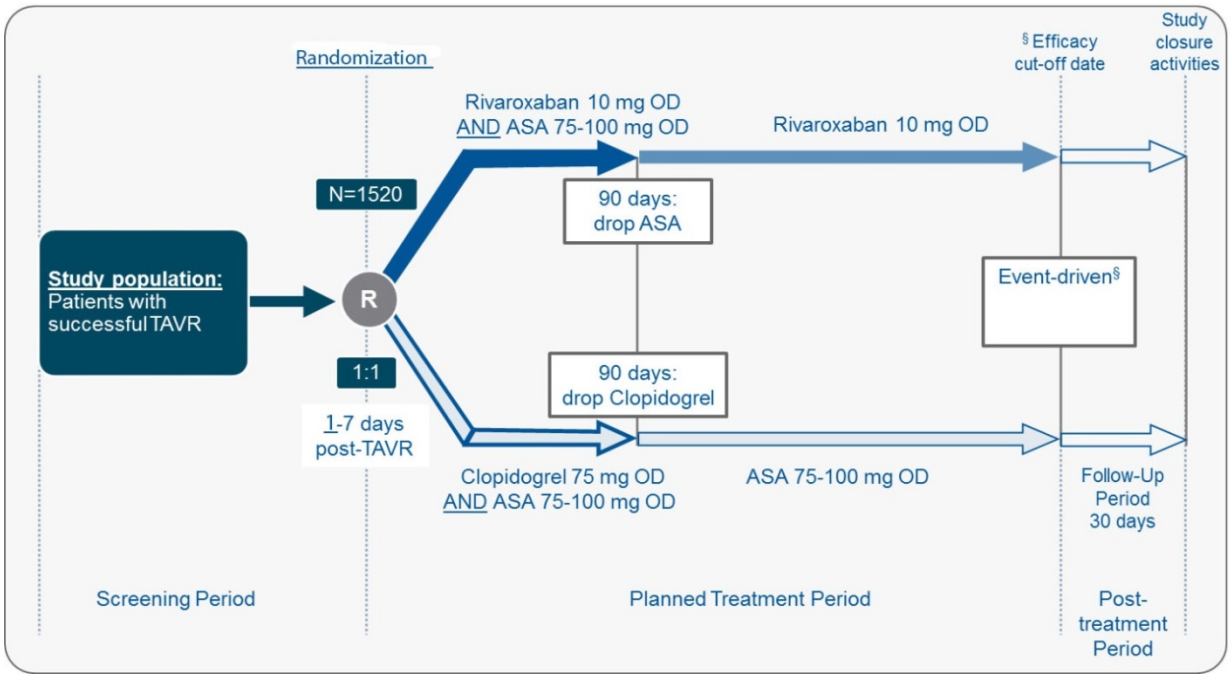
This section was changed as a result of Modifications 4 and 12.

*Old text:*




Successful transcatheter aortic valve replacement (TAVR) as defined in Section 6.1.
§ 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. 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.

*New text:*




Successful transcatheter aortic valve replacement (TAVR) as defined in Section 6.1.
§ 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.

### 15.2.2.6. Section 5.2 Study plan

This section was changed as a result of Modifications 1, 2, and 4.

*Old text:*

….

The screening period begins after TAVR. Subjects who have successfully undergone a TAVR procedure of ~~a native~~ aortic valve stenosis by iliofemoral or subclavian access with any approved/marketed device type available in the participating countries are potentially eligible for inclusion in the study. ….

….

Randomization must take place within ~~2~~-7 days post-TAVR and before hospital discharge. Randomization is performed by an Interactive Web or Voice Response System (IxRS) and stratified by site. Stratification by site is performed to ensure balance across potential local differences in treatment practices.

….

The assigned treatment strategy is implemented after randomization ~~without any undue delay~~ (please refer to Section 7.4).

Subjects randomized to rivaroxaban-based strategy: In the rivaroxaban-based strategy, rivaroxaban is started at the time of randomization if the subject is not on clopidogrel. If the subject is treated with clopidogrel, clopidogrel is stopped immediately after randomization and rivaroxaban is started within ~~24-72 hours~~ after the last intake of clopidogrel. ….

*New text*:

….

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) by iliofemoral or subclavian access with any approved/marketed device type available in the participating countries are potentially eligible for inclusion in the study. ….

….

Randomization must take place within 1-7 days post-TAVR and before hospital discharge. Randomization is performed by an Interactive Web or Voice Response System (IxRS) and stratified by site. Stratification by site is performed to ensure balance across potential local differences in treatment practices.

….

The assigned treatment strategy is implemented after randomization (please refer to Section 7.4).

Subjects randomized to rivaroxaban-based strategy: In the rivaroxaban-based strategy, rivaroxaban is started at the time of randomization if the subject is not on clopidogrel. If the subject is treated with clopidogrel, clopidogrel is stopped immediately after randomization and rivaroxaban is started within 1-3 days after the last intake of clopidogrel. In case study medication is started the next day post-TAVR, study medication should not be started earlier than the time the TAVR was done on the previous day and the subject should be stabilized and complication or bleedings should have been excluded carefully. ….

## 15.2.2.7. Section 5.3.3 Other variable(s)

This section was changed as a result of Modification 12.

*Old text:*

….

The primary completion event for this study occurs when the 440$^{th}$ subject experiences a positively adjudicated primary efficacy endpoint. The efficacy cut-off date is defined as the date of the primary completion event.

For practical purposes, the anticipated efficacy cut-off date is set based on a projection of the date of the primary completion event ~~after~~ 400 subjects have experienced a positively adjudicated primary efficacy endpoint. When the anticipated efficacy cut-off date is set, ~~an~~ on-site visit will be scheduled for all subjects within 6 weeks.

….

*New text:*

….

The primary completion event for this study occurs when the 440th subject experiences a positively adjudicated primary efficacy endpoint or earlier if the event rate is unexpectedly low. The efficacy cut-off date is defined as the date of the primary completion event.

For practical purposes, the anticipated efficacy cut-off date is set based on a projection of the date of the primary completion event before 400 subjects have experienced a positively adjudicated primary efficacy endpoint. When the anticipated efficacy cut-off date is set, on-site visit will be scheduled for all subjects within 6 weeks.

….

### 15.2.2.8. Section 6.1 Inclusion criteria

This section was changed as a result of Modification 2.

*Old text:*

Potential subjects must satisfy the following criteria to be enrolled in the study:

….

- Have a successful TAVR of ~~a native~~ aortic valve stenosis

….

**Successful TAVR (29) is defined:**

**….**

2. Intended performance of the prosthetic heart valve - presence of all 3 conditions post-TAVR:
   a. mean aortic valve gradient < 20 mmHg
   b. peak transvalvular velocity < 3.0 m/s
   c. no severe or moderate aortic valve regurgitation
3. Absence of periprocedural complications, such as:
   a. Any type of stroke

….

*New text:*

Potential subjects must satisfy the following criteria to be enrolled in the study:

….

- Have a successful TAVR of an aortic valve stenosis (either native or valve-in-valve)

….

**Successful TAVR (29) is defined:**

**….**

2. Intended performance of the prosthetic heart valve - presence of all 3 conditions post-TAVR:
   a. mean aortic valve gradient < 20 mmHg
   b. peak transvalvular velocity (aortic valve maximum velocity) < 3.0 m/s
   c. no severe or moderate aortic valve regurgitation
3. Absence of periprocedural complications, such as:
   a. Any type of periprocedural stroke

….

### 15.2.2.9. Section 6.2 Exclusion criteria

This section was changed as a result of Modifications 3 and 6.

*Old text:*

Subjects are NOT eligible to participate in this trial if they meet ANY of the following exclusion criteria:

**….**

**Concomitant and study medication**

4. Any indication for dual-antiplatelet therapy (DAPT) ~~for more than 3 months after randomization~~ (such as coronary, carotid or peripheral stent implantation)

….

**Concomitant conditions**

….

15. Active malignancy (diagnosed within 5 years) except for adequately treated non-melanoma skin cancer or other non-invasive or in situ neoplasm (e.g., cervical cancer in situ that has been successfully treated)

*New text:*

Subjects are NOT eligible to participate in this trial if they meet ANY of the following exclusion criteria:

**….**

**Concomitant and study medication**

4. Any ongoing absolute indication for dual-antiplatelet therapy (DAPT) at time of screening that is unrelated to the TAVR procedure

….

**Concomitant conditions**

….

15. Active malignancy (diagnosed within 5 years) except for adequately treated non-melanoma skin cancer or other non-invasive or in situ neoplasm (e.g., cervical cancer in situ that has been successfully treated or non-active prostate cancer)

## 15.2.2.10. Section 7.1.1 Rivaroxaban-based strategy (experimental strategy)

This section was changed as a result of Modification 1.

*Old text:*

….

The first dose of rivaroxaban is given ~~immediately after~~ randomization or within ~~24-72 hours~~ after the last intake of clopidogrel. ….

*New text:*

….

The first dose of rivaroxaban is given at the time of randomization if the subject is not on clopidogrel or within 1-3 days after the last intake of clopidogrel. In case study medication is started the next day post-TAVR, study medication should not be started earlier than the time the TAVR was done on the previous day and the subject should be stabilized and complication or bleedings should have been excluded carefully.….

## 15.2.2.11. Section 7.6 Drug logistics and accountability

This section was changed as a result of Modifications 14 and 16.

*Old text:*

Rivaroxaban will be stored at the investigational site in accordance with GCP and GMP requirements and according to the instructions given by the clinical supplies department of the sponsor (or its affiliate/CRO), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of rivaroxaban via IxRS. The study personnel will use rivaroxaban only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of rivaroxaban must be properly documented according to the sponsor's agreed and specified procedures. Re-supply of rivaroxaban ~~can be~~ initiated through the IxRS module in the eCRF.

*New text:*

Rivaroxaban will be stored at the investigational site in accordance with GCP and GMP requirements and according to the instructions given by the clinical supplies department of the sponsor (or its affiliate/CRO/academic research organization [ARO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of

batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of rivaroxaban via IxRS. The study personnel will use rivaroxaban only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of rivaroxaban must be properly documented according to the sponsor's agreed and specified procedures. Re-supply of rivaroxaban is automatically initiated through the IxRS module in the eCRF.

## 15.2.2.12. Section 8.1 Prior and concomitant therapy

This section was changed as a result of Modification 7.

*Old text:*

All medications (prescription and over-the-counter), including adjunct therapy or medical devices, will be recorded in the appropriate section of the eCRF throughout the study.

….

- Medicines that reduce gastric acid (e.g., H-2 antagonists or proton pump inhibitors [PPIs]) may reduce the incidence of GI bleeding in subjects' post-TAVR who are treated with antithrombotics and unless contraindicated their use is recommended. The choice of gastric protection drugs (such as pantoprazole) is at the discretion of the treating physician. PPIs that interact with cytochrome P450 2C19 (such as omeprazole or esomeprazole) are disallowed.

Concomitant use (with study treatment strategies) of the following therapies is disallowed during the study:

- Single or dual antiplatelet therapy other than assigned study strategy
- ~~In the rivaroxaban-based strategy use of P2Y12 inhibitors in combination with rivaroxaban.~~
- ~~In the antiplatelet-based strategy, the use of a P2Y12 inhibitor for > 3 months (> 90 days) after randomization.~~
- VKA other than the assigned study strategy and low molecular weight or unfractionated heparin if used for reasons other than short-term bridging of VKA therapy until the target INR is established.
- Factor IIa inhibitors and factor Xa inhibitors other than the study medication
- ~~Systemic treatment with drugs that are strong inhibitors of both CYP 3A4 and P-gp (azole-antimycotics such as ketoconazole and itraconazole or HIV protease inhibitors such as ritonavir). The azole-antimycotic fluconazole, a moderate CYP 3A4 inhibitor, has however less effect on rivaroxaban exposure and can be co-administered.~~
- ~~Systemic treatment with drugs that are strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's wort).~~

- ~~Concomitant therapy with omeprazole or esomeprazole that cannot be switched to an alternative medication.~~

….

*New text:*

All ongoing medications at screening and used during the study (prescription and over-the-counter), including adjunct therapy or medical devices, will be recorded in the appropriate section of the eCRF throughout the study. Use of ASA and clopidogrel or any other P2Y12 inhibitor prior and during TAVR procedure should also be recorded.

….

- Medicines that reduce gastric acid (e.g., H-2 antagonists or proton pump inhibitors [PPIs]) may reduce the incidence of GI bleeding in subjects' post-TAVR who are treated with antithrombotics and unless contraindicated their use is recommended. The choice of gastric protection drugs (such as pantoprazole) is at the discretion of the treating physician. PPIs that interact with cytochrome P450 2C19 (such as omeprazole or esomeprazole) are disallowed in the antiplatelet-based strategy, during concomitant use of clopidogrel.

Concomitant use (with study treatment strategies) of the following therapies is disallowed during the study:

- Single or dual antiplatelet therapy other than assigned study strategy
- VKA other than the assigned study strategy and low molecular weight or unfractionated heparin if used for reasons other than short-term bridging of VKA therapy until the target INR is established
- Factor IIa inhibitors and factor Xa inhibitors other than the study medication
- In the rivaroxaban-based strategy concomitant use of
    - P2Y12 inhibitors in combination with rivaroxaban
    - During concomitant use of rivaroxaban systemic treatment with drugs that are strong inhibitors of both CYP 3A4 and P-gp (azole antimycotics such as ketoconazole and itraconazole or HIV protease inhibitors such as ritonavir). The azole antimycotic fluconazole, a moderate CYP 3A4 inhibitor, has however less effect on rivaroxaban exposure and can be co-administered.
    - During concomitant use of rivaroxaban systemic treatment with drugs that are strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's wort)
- In the antiplatelet-based strategy concomitant use of
    - P2Y12 inhibitor for > 3 months (> 90 days) after randomization
    - Omeprazole or esomeprazole that cannot be switched to an alternative medication during concomitant use of clopidogrel

### 15.2.2.13. Section 9.1 Tabular schedule of evaluations

This section was changed as a result of Modifications 4, 9, 10, 11, 12, and 14.

*Old text:*

**Table 1: Schedule of evaluations**

| **Visit number** | | **1** | **2** | **3** | **4** | **5** | **6, 7, (n)** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Screening** | | **Planned treatment** | | | | | | **Post-treatment** |
| **Visit** | **Screening** | **Baseline / Randomization[b]** | **On-site visit** | **On-site visit** | **Phone call** | **On-site visit** | **On-site visit** | **On-site visit** | **Phone call** |
| **Day** | **~~2~~-7 days [a] ~~prior to randomization~~** | **~~0~~** | **30** | **90** | **180 [c]** | **360 [c]** | **540,720[c], z** | | |
| | | | | | | | **every 180d** | **EOT [d]** | **EOT+30d [e]** |
| **Window (day[s])** | | | **± 7d** | **± 15d** | **± 15d** | **± 30d** | **± 30d** | **[d]** | **± 7d** |
| **Study Assessments** | | | | | | | | | |
| Informed consent [a] | X | | | | | | | | |
| Demographics [f] | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Prior medication | X | | | | | | | | |
| TAVR assessment | X | | | | | | | | |
| In /exclusion criteria | X | X | | | | | | | |
| Concomitant medication | | X | X | X | X | X | X | X | X |
| Physical exam | | X | X | X | | X | X | X | |
| Vital signs [g] | | X | X | X | | X | X | X | |
| Echocardiogram (TTE or TEE) [h] | X | | | | | X | | | |
| 12-lead ECG | | X | X | X | | X | X | X | |
| **Study Medication** | | | | | | | | | |
| Prescribing/dispensing assigned strategy | | X [i] | X | X | | X | X | | |
| Treatment strategy adjustment [j] | | | | X | | | | | |

| **Visit number** | | **1** | **2** | **3** | **4** | **5** | **6, 7, (n)** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Screening** | | **Planned treatment** | | | | | | **Post-treatment** |
| **Visit** | **Screening** | **Baseline / Randomization[b]** | **On-site visit** | **On-site visit** | **Phone call** | **On-site visit** | **On-site visit** | **On-site visit** | **Phone call** |
| **Day** | **~~2~~-7 days [a] ~~prior to randomization~~** | **~~0~~** | **30** | **90** | **180 [c]** | **360 [c]** | **540,720[c], z** | | |
| | | | | | | | **every 180d** | **EOT [d]** | **EOT+30d [e]** |
| **Window (day[s])** | | | **± 7d** | **± 15d** | **± 15d** | **± 30d** | **± 30d** | **[d]** | **± 7d** |
| Transition to other therapy | | | | | | | | X | |
| **Laboratory Assessments (local labs)** | | | | | | | | | |
| Hematology [k] | X | | | | | | | | |
| Liver tests [L] | X | | | | | | | | |
| Renal function [m] | X | | | | | | | | |
| **Ongoing study assessments** | | | | | | | | | |
| Efficacy endpoints | | X | X | X | X | X | X | X | X |
| Safety endpoints | | X | X | X | X | X | X | X | X |
| NOAF assessment and adjustment of treatment [n] | | X | X | X | X | X | X | X | X |
| (Serious) AEs [o] | X | X | X | X | X | X | X | X | X |

[a] Consenting subjects must be randomized within ~~2~~ 7 ~~calendar~~ days post-TAVR and before hospital discharge.

[b] Once randomized, a subject has entered the study and all randomized subjects will be followed until the efficacy cut-off date when the predefined number of efficacy endpoints is anticipated, even if they did not take assigned study medication or prematurely discontinued study medication. In case of early permanent discontinuation of study medication, all relevant information must be captured in the eCRF as soon as possible after stopping the assigned study medication. The timing of on-site visits and of telephone contacts must be kept unchanged.

....

[L] Liver tests include transaminases (AST/ALT), total bilirubin and its components (conjugated and unconjugated fractions), and alkaline phosphatase.

....

[o] For details, see Section 9.6.1.4 and 9.6.1.6. Only SAEs or AEs that lead to permanent discontinuation of the assigned study medication are to be reported. The investigator must report immediately (within 24 hours of the investigator's awareness) all (S)AEs as described in Figure 3.

*New text:*

**Table 1: Schedule of evaluations**

| **Visit number** | | **1** | **2** | **3** | **4** | **5** | **6, 7, (n)** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Screening** | | **Planned treatment** | | | | | | **Post-treatment** |
| **Visit** | **Screening** | **Baseline / Randomization[b]** | **On-site visit** | **On-site visit** | **Phone call** | **On-site visit** | **On-site visit** | **On-site visit** | **Phone call** |
| **Day** | **1-7 days [a] post-TAVR** | | **30** | **90** | **180 [c]** | **360 [c]** | **540,720[c], z** | | |
| | | | | | | | **every 180d** | **EOT [d]** | **EOT+30d [e]** |
| **Window (day[s])** | | | **±7d** | **± 15d** | **± 15d** | **± 30d** | **± 30d** | **[d]** | **± 7d** |
| **Study Assessments** | | | | | | | | | |
| Informed consent [a] | X | | | | | | | | |
| Demographics [f] | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Prior medication | X | | | | | | | | |
| TAVR assessment | X | | | | | | | | |
| In /exclusion criteria | X | X | | | | | | | |
| Concomitant medication | | X | X | X | X | X | X | X | X |
| Physical exam [p] | | X | X | X | | X | X | X | |
| Vital signs [g] | | X | X | X | | X | X | X | |
| Echocardiogram (TTE or TEE) [h] | X | | | | | X | | | |
| 12-lead ECG | | X | X | X | | X | X | X | |
| **Study Medication** | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Prescribing/dispensing assigned strategy | | X [i] | X | X | | X | X | | |
| Treatment strategy adjustment [j] | | | | X | | | | | |
| Transition to other therapy | | | | | | | | X | |
| **Laboratory Assessments (local labs)** | | | | | | | | | |
| Hematology [k] | X | | | | | | | | |
| Liver tests [L] | X | | | | | | | | |
| Renal function [m] | X | | | | | | | | |
| **Ongoing study assessments** | | | | | | | | | |
| Efficacy endpoints | | X | X | X | X | X | X | X | X |
| Safety endpoints | | X | X | X | X | X | X | X | X |
| NOAF assessment and adjustment of treatment [n] | | X | X | X | X | X | X | X | X |
| (Serious) AEs [o] | X | X | X | X | X | X | X | X | X |
| Vital status | | | | | | | | | |

[a] Consenting subjects must be randomized within 1-7 days post-TAVR and before hospital discharge.

[b] Once randomized, a subject has entered the study and all randomized subjects will be followed until the efficacy cut-off date when the predefined number of efficacy endpoints is anticipated or earlier if the event rate is unexpectedly low, even if they did not take assigned study medication or prematurely discontinued study medication. In case of early permanent discontinuation of study medication, all relevant information must be captured in the eCRF as soon as possible after stopping the assigned study medication. The timing of on-site visits and of telephone contacts must be kept unchanged.

....

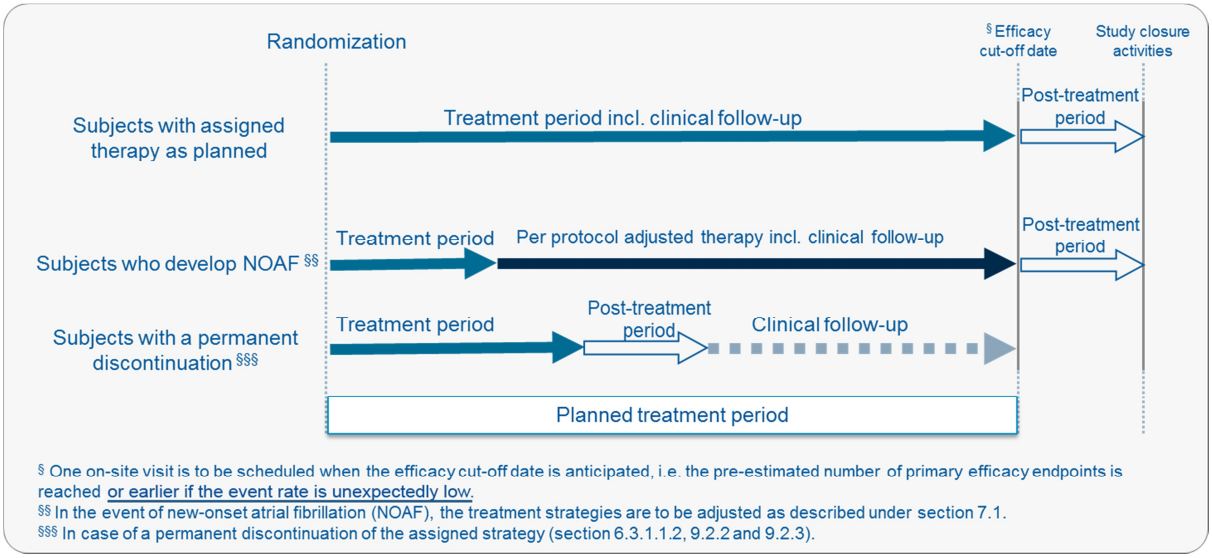
[L] Liver tests include transaminases (AST/ALT), total bilirubin and its components (conjugated and/or unconjugated fractions) in case of elevated total bilirubin, and alkaline phosphatase if available as current standard of care. Liver test results collected before TAVR procedure can be used as long as performed as part of the standard of care for the index-TAVR procedure.

[o] For detail, See section 9.6.1.4 and 9.6.1.6. Only SAEs, AE of special interest (even if classified as non-serious), or AEs that lead to permanent discontinuation of the assigned study medication are to be reported. The investigator must report immediately (within 24 hours of the investigator's awareness) all (S)AEs as described in Figure 3.

[p] Physical examination aims to investigate any occurrence of a safety or efficacy outcome.

*Added text:*

**Figure 2: Study treatment flow diagram.**




## 15.2.2.14. Section 9.2.1 Screening period (screening and randomization)

This section was changed as a result of Modifications 4, 10, 14, and 15.

*Old text:*

…. Please note that if screening procedures are performed as part of routine medical practice (e.g. laboratory parameters) these are not required to be repeated as long as they ~~are within the screening window~~.

~~Screening evaluations are performed after the index-TAVR procedure (between 2 and 7 calendar days after the subject index-TAVR procedure). All screening procedures are completed before randomization on Day 0.~~ Before the IC form is obtained the inclusion and exclusion criteria are reviewed to assess the subjects' eligibility. ~~All clinical laboratory results performed during screening are used to confirm eligibility for randomization~~.

….

Randomization by IxRS, must take place within ~~2~~-7 days post-TAVR, and before hospital discharge. The allocated treatment strategy is implemented after randomization ~~without any undue delay~~.

If allowed by the subject, his/her general practitioner (GP) will be informed of the subject's participation in the trial by means of a letter from the investigator. Information will be included on the treatment strategies as well as on specific clinical assessments that must come to the attention of the investigational study center before subject's treatment is modified (such as, if NOAF is detected).

**Screening (~~2~~-7 days ~~prior to randomization~~)**

The following procedures will be performed ~~2~~-7 ~~calendar~~ days after the index-TAVR and **prior to randomization**:

….

**Visit 1 – Baseline / Randomization - ~~Study Day 0~~**

….

- 12-lead electrocardiogram (ECG)

….

The following procedures will be performed ~~2~~-7 ~~calendar~~ days after the index-TAVR, **after randomization and before discharge**:

….

*New text:*

…. Please note that if screening procedures are performed as part of routine medical practice (e.g. laboratory parameters) these are not required to be repeated as long as they meet the protocol requirements described below.

Hematology tests and renal function results from standard of care can be used as long as collected after the index-TAVR procedure and before randomization. Liver test results collected before TAVR procedure can be used as long as performed as part of the standard of care for the index-TAVR procedure. Before the IC form is obtained the inclusion and exclusion criteria are reviewed to assess the subjects' eligibility.

….

Randomization by IxRS, must take place within 1-7 days post-TAVR, and before hospital discharge. The allocated treatment strategy is implemented after randomization.

If allowed by the subject or for local legal requirements, his/her general practitioner (GP) will be informed of the subject's participation in the trial by means of a letter from the investigator. Information will be included on the treatment strategies as well as on specific clinical assessments that must come to the attention of the investigational study center before subject's treatment is modified (such as, if NOAF is detected).

**Screening (1-7 days post-TAVR)**

The following procedures will be performed 1-7 days after the index-TAVR and **prior to randomization**:

….

**Visit 1 – Baseline / Randomization**

**….**

- 12-lead electrocardiogram (ECG) or any other method documenting heart rhythm (e.g. ECG strip) able to exclude atrial fibrillation

….

The following procedures will be performed 1-7 days after the index-TAVR, **after randomization and before discharge**:

….

## 15.2.2.15. Section 9.2.2 Planned treatment period

This section was changed as a result of Modifications 4 and 12.

*Added text:*

The duration of the planned treatment period for a given subject will depend on the time needed to reach the efficacy cut-off date, i.e. to collect the predefined number of primary adjudicated efficacy endpoints in the total study population or earlier if the event rate is unexpectedly low. The expected duration of the treatment period is 720 days but may be longer or even shorter depending upon the rate of subject recruitment and efficacy event rates. Visits are scheduled at 30, 90, 180 days after randomization, and every 180 days thereafter until the anticipated efficacy cut-off date is set (see Section 9.1 Tabular schedule of evaluations (Table 1)) at which time a final on-site visit will be scheduled.

## 15.2.2.16. Section 9.2.3 Post-treatment period

This section was changed as a result of Modification 9.

*Added text:*

**End of study visit**

This visit takes place within 6 weeks of the announcement of the anticipated efficacy cut-off date.

This visit will be performed for subjects who early permanent discontinue the study medication and had the expectation to keep the regular scheduled visits as planned by the time of study drug discontinuation. This visit will also be performed for subjects who withdraw consent and allow collection of further information.

The following procedures will be performed during this visit:

- Assess if any efficacy and/or safety endpoints occurred
- Vital status, if applicable
- Assessment of (S)AEs

## 15.2.2.17. Section 9.6.3.1 Laboratory evaluation

This section was changed as a result of Modification 10.

*Old text:*

The following local routine laboratory measurements need to be ~~performed post-TAVR and~~ before randomization.

….

- Liver tests
    - Transaminases (AST/ALT)
    - Total bilirubin and components (conjugated and unconjugated fractions)
    - Alkaline phosphatase

*New text:*

The following local routine laboratory measurements need to be evaluated before randomization.

….

- Liver tests
    - Transaminases (AST/ALT)
    - Total bilirubin and components (conjugated and/or unconjugated fractions in case of elevated total bilirubin)
    - Alkaline phosphatase, if available as current standard of care

….

Laboratory tests results done as part of standard of care can be used. Hematology tests and renal function results from standard of care can be used as long as collected after the index-TAVR procedure and before randomization. Liver test results collected before TAVR procedure can be used as long as performed as part of the standard of care for the index-TAVR procedure.

## 15.2.2.18. Section 10.2.2 Data scope

This section was changed as a result of Modification 12.

*Deleted text:*

….

**Data scope after NOAF (post-NOAF analysis)**

The post-NOAF data scope includes all outcome events observed between the treatment switch precipitated by NOAF until the efficacy cut-off date ~~(i.e. EOT visit performed)~~.

## 15.2.2.19. Section 10.3.4 Subgroup variables

This section was changed as a result of Modification 12.

*Added text:*

…

- Valve-in-valve procedure

## 15.2.2.20. Section 10.3.5 Planned statistical analysis

This section was changed as a result of Modification 12.

*Deleted text:*

~~10.3.5 Planned statistical analysis~~

~~The primary efficacy and safety endpoints are analyzed as a time-to-event endpoint, using the Cox proportional hazards model. The validity of the proportional hazards assumption will be assessed prior to carrying out the analysis. Kaplan-Meier curves are used to describe the occurrence of the primary efficacy endpoint over time.~~

## 15.2.2.21. Section 10.3.5 Analysis of the primary efficacy variable

This section was changed as a result of Modification 12.

*Old text:*

### ~~10.3.5.1~~ Analysis of the primary efficacy variable

The analysis of the primary efficacy variable is performed on the Full Analysis Set (FAS) ~~under the ITT scope – that is, events are analyzed irrespective of their time of occurrence relative to termination of assigned study treatment strategy. Follow-up is censored at the last date of known outcome status or at the efficacy cut-off date, whichever comes first.~~

*New text:*

### 10.3.5 Analysis of the primary efficacy variable

The analysis of the primary efficacy variable is performed on the Full Analysis Set (FAS). For superiority analysis the follow-up is censored at the last date of known outcome status or at the efficacy cut-off date, whichever comes first. Non-inferiority analysis is carried out under the OT data scope, i.e. follow-up is censored at two days after permanent discontinuation of the randomized treatment strategy. Censoring is assumed independent of the treatment group assignment.

## 15.2.2.22. Section 10.3.5.1.1 Test for validity of the proportional hazard assumption

This section was changed as a result of Modification 12.

*Deleted text:*

### ~~10.3.5.1.1 Test for validity of the proportional hazard assumption~~

~~The validity of the proportional hazards assumption is assessed with the use of the test proposed by Grambsch and Therneau on the Schoenfeld residuals (estat ph test) (60).~~

~~If the assumption of proportional hazards holds, superiority of the rivaroxaban-based strategy for the primary outcome is tested with the use of the Hazard Ratio (HR) and the Cox proportional hazards model. The test for superiority is hierarchically preceded by a test for non-inferiority with a non-inferiority boundary of 1.20 for the hazard ratio.~~

~~In case of rejection of the assumption of proportional hazards for the primary efficacy endpoint, superiority of the rivaroxaban-based strategy for the primary outcome is tested with the use of the log rank methodology, without any (preceding) testing for non-inferiority.~~

## 15.2.2.23. Section 10.3.5.1 Testing for superiority

This section was changed as a result of Modification 12.

***Old text:***

### 10.3.5.1.2 Testing for superiority ~~under the proportional hazards assumption~~

~~If the assumption of proportional hazards holds, superiority of the rivaroxaban-based strategy for the primary outcome is tested with the use of the hazard ratio (HR) and the Cox proportional hazards model. The HR(t) at time t is defined as:~~

> ~~$HR(t) = \lambda(t)_{rivaroxaban} / \lambda(t)_{antiplatelet}$, where $\lambda(t)$ is the hazard of the primary efficacy endpoint, respectively in subjects randomized to the rivaroxaban-based strategy and in subjects randomized to the antiplatelet-based strategy.~~

~~Under the proportional hazards assumption, $\lambda(t)$ may vary over time, but the ratio of the two hazards is constant.~~

~~The following null hypothesis ($H_0$) is tested at a one-sided significance level of 0.025%:~~

> ~~$H_0$: $HR(t) = 1$ 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 to the hazard (= instantaneous risk) for the primary efficacy endpoint at all time points")~~

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

> ~~$H_1$: $HR(t) < 1$ for all time points $t \geq 0$, (i.e. "there is difference in favor of the rivaroxaban-based treatment group for the primary efficacy endpoint at all time points")~~

The parameter estimate β (=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 decision rule to test the null hypothesis is applied:~~

> ~~If the z value from the one-sided test for the HR ($\beta_{ML}/SE(\beta)_{ML}$) is smaller than the critical quantile from the normal distribution ($z_{0.025} = -1.96$), the null hypothesis is rejected in favor of the alternative hypothesis.~~

~~Or, equivalently, if the 95% Confidence Interval for HR falls below 1.00.~~

~~This test is~~ carried out under the ITT data scope (i.e. all events are counted irrespective of the actual treatment at the time of the event).

***New text:***

**10.3.5.1 Testing for superiority**

In order to evaluate whether the rivaroxaban-based strategy is superior to the antiplatelet-based strategy in prolonging the time to primary efficacy outcome event in patients with post-TAVR patients, the following null hypothesis ($H_0$) is tested 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 outcome for all time points")

The one-sided alternative hypothesis 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 a difference between the two groups in favor of the rivaroxaban-based treatment group regarding the primary efficacy outcome for at least one time point")

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 estimates of cumulative risk and cumulative hazard functions 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.

Hazard ratio and corresponding two-sided 95% confidence intervals are estimated based on a Cox proportional hazards models. The parameter estimate $\beta$ (=ln(HR)), its standard error, p-value, and 95% Confidence Limits are calculated according to the maximum partial likelihood method, with Breslow's approximation for ties (phreg).

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

All of the above analyses are carried out under the ITT data scope (i.e. all events are counted irrespective of the actual treatment at the time of the event).

Further details will be specified in SAP.

## 15.2.2.24. Section 10.3.5.2 Testing for non-inferiority

This section was changed as a result of Modification 12.

***Old text:***

~~10.3.5.1.3~~ **Testing for non-inferiority ~~under the proportional hazards assumption~~**

~~If the assumption of proportional hazards holds, testing for superiority of the rivaroxaban-based strategy for the primary efficacy outcome is preceded by testing for non-inferiority tested with the use of the hazard ratio (HR) and the Cox proportional hazards model.~~

The following ~~an~~ (inferiority) null hypothesis ($H_0$) is tested at a one-sided significance level of 2.5%:

> $H_0$: HR(t) $\geq$ 1.2~~0~~ 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:

> $H_1$: HR(t) < 1.2~~0~~ 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 HR is below 1.20")

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

> If the upper boundary of 95% confidence interval (CI) for HR falls below 1.20, 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.

In order to preserve the type I error rate for efficacy testing, the two tests for the primary efficacy endpoint are technically placed in a hierarchical order, (1) testing for non-inferiority as described in this section followed by (2) testing for superiority as described in the previous section.

~~This test is carried out under the OT data scope (i.e. follow-up is censored at two days after permanent discontinuation of the randomized treatment strategy; in other words, only those events that occurred between randomization and two days after permanent discontinuation of the randomized treatment strategy are analyzed).~~

***New text:***

**<u>10.3.5.2</u> Testing for non-inferiority**

<u>Using a log rank test adapted to non-inferiority testing</u> the following (inferiority) null hypothesis ($H_0$) is tested at a one-sided significance level of 2.5%:

> $H_0$: HR(t) $\geq$ 1.2 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:

$H_1$: HR(t) < 1.2 for all time points t ≥ 0, (i.e. "the hazard in the rivaroxaban-based treatment group for the primary efficacy endpoint is such that the HR is below 1.20")

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

If the upper boundary of 95% confidence interval (CI) for HR falls below 1.20, 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.

Hazard ratio and corresponding two-sided 95% confidence intervals are estimated based on a Cox proportional hazards model.

In order to preserve the type I error rate for efficacy testing, the two tests for the primary efficacy endpoint are technically placed in a hierarchical order, (1) testing for non-inferiority as described in this section followed by (2) testing for superiority as described in the previous section.

## 15.2.2.25. Section 10.3.5.1.4 Testing for superiority in case of rejection of the proportional hazards assumption

This section was changed as a result of Modification 12.

***Deleted text:***

~~**10.3.5.1.4 Testing for superiority in case of rejection of the proportional hazards assumption**~~

~~In case of rejection of the assumption of proportional hazards for the primary efficacy endpoint, superiority of the rivaroxaban-based strategy for the primary outcome is tested with the use of the log rank-methodology, without any (preceding) testing for non-inferiority.~~

~~The following null hypothesis ($H_0$) is tested one-sided at the significance level of 2.5%:~~

~~$H_0$: ***SR(t)*** = ***SA(t)*** for all time points ***t*** ≥ 0, (i.e. "there is no difference between the rivaroxaban-based treatment group and the ASA-based control group regarding the primary efficacy outcome for all time points")~~

~~The one-sided alternative hypothesis is:~~

~~$H_1$: ***SR(t)*** > ***SA(t)*** for at least one time point ***t*** ≥ 0, and ***SR(t)*** ≥ ***SA(t)*** for all time points ***t*** ≥ 0, (i.e. "there is a difference between the two groups in favor of rivaroxaban regarding the primary efficacy outcome for at least one time point")~~

~~where ***SR*** denotes the survival function of the rivaroxaban and ***SA*** denotes the survival function of the ASA-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 stratified log-rank test to the normal distribution. If the z-value from the one-sided log-rank test (for the difference ***SR(t) - SA(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.~~

~~This test is carried out under the ITT data scope (i.e. all events are counted irrespective of the actual treatment at the time of the event).~~

## 15.2.2.26. Section 10.3.5.3 Exploratory analyses of the primary efficacy variable

This section was changed as a result of Modification 12.

*Old text:*

**~~10.3.5.1.5~~ Exploratory analyses of the primary efficacy variable**

*New text:*

**10.3.5.3 Exploratory analyses of the primary efficacy variable**

## 15.2.2.27. Section 10.3.6 Analysis of secondary and other efficacy variable

This section was changed as a result of Modification 12.

*Old text:*

**~~10.3.5.2~~ Analysis of secondary and other efficacy variable**

*New text:*

**10.3.6 Analysis of secondary and other efficacy variable**

## 15.2.2.28. Section 10.3.7 Analysis of safety variables

This section was changed as a result of Modification 12.

*Old text:*

### ~~10.3.5.3~~ Analysis of safety variables

The analysis of the primary safety variable is performed on the Full Analysis Set (FAS) under the ITT data scope — that is, events are analyzed irrespective of their time of occurrence relative to termination of assigned study treatment strategy. Follow-up is censored at the last date of known outcome status or at the efficacy cut-off date, whichever comes first.

~~The analysis of primary safety variable is that of a non-inferiority design with a non-inferiority boundary of 1.50. Hypotheses and analytic methods are similar to those described in Section 10.3.5.2. Non-inferiority for the primary safety variable is established if the upper-bound of the 95% confidence interval for the hazard ratio for the primary safety variable falls below 1.50.~~

On treatment analyses, pre-NOAF and post-NOAF analyses of the primary safety variable are performed as exploratory analyses.

The analyses of secondary safety variables are similar to those for secondary efficacy variables, without any sequential order.

*New text:*

**10.3.7 Analysis of the safety variables**

The analysis of the primary safety variable is performed on the Full Analysis Set (FAS) under the ITT data scope — that is, events are analyzed irrespective of their time of occurrence relative to termination of assigned study treatment strategy. Follow-up is censored at the last date of known outcome status or at the efficacy cut-off date, whichever comes first.

Kaplan-Meier estimates of cumulative risk and cumulative hazard functions for the primary safety variable 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.

If the proportional hazards assumption holds for the primary safety variable, hazard ratio and corresponding two-sided 95% confidence intervals are estimated based on a Cox proportional hazards models.

On treatment analyses, pre-NOAF and post-NOAF analyses of the primary safety variable are performed as exploratory analyses.

All of the above analyses of the primary safety variable are descriptive, without formal statistical tests being performed.

The analyses of secondary safety variables are similar to those for secondary efficacy variables, without any sequential order.

## 15.2.2.29. Section 10.3.8 Subgroup analysis

This section was changed as a result of Modification 12.

*Old text:*

**~~10.3.5.4~~ Subgroup analysis**

*New text:*

**10.3.8 Subgroup analysis**

## 15.2.2.30. Section 10.4 Determination of sample size

This section was changed as a result of Modification 12.

*Old text:*

….

A sample size of sample size of 2 x 760 subjects allows for an attrition rate of 2.63%. The study is event driven and the number of randomized subjects is estimated to be required to collect 440 primary efficacy events. The study is planned to run until this number of events has been reached.

….

The final sample size will depend on multiple factors including the rate of accrual of the primary endpoint events. ~~Therefore, the sample size may be increased if planning assumptions are modified based on blinded data review.~~ The Steering Committee of the trial will monitor the aggregate (blinded) event rate and may increase the sample size or duration of follow-up to achieve the planned target number of events in consultation with the sponsor.

….

Taking into consideration both the historical NI margins used in TAVR trials together with the expected high event rates and the considerable proportion of subjects with NOAF after randomization, a ~~conservative~~ non-inferiority margin of 1.20 was chosen for this study.

~~**Power analysis for safety**~~

~~The expected 540 days event rate of the primary safety endpoint is 12.0% (5, 7, 12, 15, 62-64). With 2 x 740 fully analyzable subjects and the accrual assumptions defined under Section 10.4 the study has 85% power to show non-inferiority with a non-inferiority margin of 1.50 for the hazard ratio at a one-sided significance level of 2.5%. The non-inferiority margin of 1.50 has been selected on basis of both clinical appropriateness and relevant studies (52).~~

~~The power calculation was based on a test using the Cox proportional hazards model and was performed with PASS version 12.0.6, with the module for two survival curves using Cox's proportional hazards model.~~

*New text:*

….

A sample size of sample size of 2 x 760 subjects allows for an attrition rate of 2.63%. The study is event driven and the number of randomized subjects is estimated to be required to collect 440 primary efficacy events. The study is planned to run until this number of events has been reached or to stop earlier if the event rate is unexpectedly low.

….

The final sample size will depend on multiple factors including the rate of accrual of the primary endpoint events. The Steering Committee of the trial will monitor the aggregate (blinded) event rate and may increase the sample size or duration of follow-up to achieve the planned target number of events in consultation with the sponsor.

….

Taking into consideration both the historical NI margins used in TAVR trials together with the expected high event rates and the considerable proportion of subjects with NOAF after randomization, a non-inferiority margin of 1.20 was chosen for this study.

## 15.2.2.31. Section 10.5 Planned interim analyses

This section was changed as a result of Modification 13.

*Old text:*

~~A planned interim analysis for futility will be performed when the last randomized subject reaches 270 days of follow-up or when 300 primary efficacy events have occurred.~~

~~The interim analysis will be performed based on adjudicated primary efficacy endpoints by treatment groups, if needed supplemented by best available information. The conditional power for the primary efficacy endpoint will be calculated. The DSMB may recommend~~

~~immediate termination of the trial if the calculated conditional power for the trial does not exceed 50%.~~

~~There will be no adjustment for type I error level for the final analysis.~~

~~The DSMB recommendation will be based on an overall assessment of benefit and harm given the observed rates of efficacy and safety endpoints at that time.~~

*New text:*

No formal interim analysis is planned.

### 15.2.2.32. Section 11.1 Data recording

This section was changed as a result of Modification 16.

*Added text:*

….

Data required according to this protocol are recorded by investigational site personnel via data entry into the internet based eCRF system, which Cardialysis (CRO) licenses from XClinical. MARVIN is validated by XClinical and Cardialysis for use in its clinical studies. MARVIN allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Cardialysis extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by XClinical and will be downloaded by Cardialysis each night. All access to the MARVIN system is through a password-protected security system that is part of the MARVIN software.

All internal Cardialysis, internal Mount Sinai (ARO), Bayer, and external investigator site personnel seeking access must go through a MARVIN training process before they are granted access to MARVIN for use in Bayer's clinical studies. Training records are maintained.

….

### 15.2.2.33. Section 11.2 Monitoring

This section was changed as a result of Modification 16.

*Added text:*

In accordance with applicable regulations, GCP, and sponsor's/CRO's/ARO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. ….

### 15.2.2.34. Section 12 Premature termination of study

This section was changed as a result of Modification 13.

*Deleted text:*

~~Results of any interim analysis~~

## 15.2.2.35. Section 16.2 Definition of terms

This section was changed as a result of Modification 14.

*Added text:*

**Non-active prostate cancer**

No current or planned diagnostic measures, chemotherapy, surgical treatment or a reduced life expectancy.

# 16. Appendices

## 16.1. Endpoint definitions

### 16.1.1. Death or first adjudicated thromboembolic event (DTE)

Defined as the composite of all-cause death and adjudicated stroke, myocardial infarction (MI), symptomatic valve thrombosis, pulmonary embolism (PE), deep vein thrombosis (DVT) or non-CNS systemic embolism.
The components of this primary efficacy endpoint are adjudicated according to the latest valve academic research consortium (VARC) definitions (29) available.

| **Death** is classified according to the VARC definitions. |
|---|
| **All-cause death**<br>• All deaths from any cause. This includes all cardiovascular and non-cardiovascular deaths. |
| **Cardiovascular death**<br>Death fulfilling any of the following criteria:<br>• Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)<br>• Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease<br>• All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure (e.g. reintervention on the operated valve)<br>• All valve-related deaths including structural or non-structural valve dysfunction or other valve-related adverse events (e.g. valve thrombosis, embolism, bleeding event, or implanted valve endocarditis)<br>• Sudden death or unwitnessed death<br>• Death of unknown cause |
| **Non-cardiovascular death**<br>• Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide) |

| **Stroke** is classified according to the VARC definitions. |
|---|
| **Diagnostic criteria**<br>• Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke<br>• Stroke – duration of a focal or global neurological deficit >24 h; OR <24 h if available neuroimaging documents, a new haemorrhage or infarct; OR the neurological deficit results in death<br>• No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumour, |

**Stroke** is classified according to the VARC definitions.

trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist*
- Confirmation of the diagnosis by at least one of the following: neurologist or neurosurgical specialist; neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

**Stroke classification**
- Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
- Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
- A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic

**Stroke definitions**
- Disabling stroke: an modified Rankin Scale (mRS) score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline
- Non-disabling stroke: an mRS score at <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline

NB: Modified Rankin Scale assessments should be made by qualified individuals according to a certification process.

* Patients with non-focal global encephalopathy will not be reported as stroke without unequivocal evidence of cerebral infarction-based upon neuroimaging studies (CT scan or brain MRI).

**Myocardial infarction (MI)** is classified according to the VARC definitions.

**Peri-procedural MI** (<72 h after the index procedure)
- New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND
- Elevated cardiac biomarkers (preferable CK-MB) within 72h after index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15x as the upper reference limit (URL) for troponin or 5x for CK-MB.

**Spontaneous MI** (> 72h after index procedure)
Any one of the following criteria:
- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99$^{th}$ percentile URL, together with the evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]
  - New pathological Q-waves in at least two contiguous leads

**Myocardial infarction (MI)** is classified according to the VARC definitions.

  - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Pathological findings of an acute myocardial infarction.

**Symptomatic valve thrombosis (29, 65)**

Symptomatic valve thrombosis is defined as any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment.
Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis. The most common clinical presentation of valve thrombosis is progressive dyspnea. The most commonly observed echocardiographic features are: increasing transvalvular gradients, thickened valve leaflets with impaired mobility and visualization of thrombus formation on the valve.

**Pulmonary embolism (PE) (66)**

Symptomatic PE was defined as objectively documented PE with one of the following findings:

- A new intraluminal filling defect in segmental or more proximal branches on sCT,
- A new intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram,
- A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy
- Inconclusive sCT, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography.
- Fatal PE based on objective diagnostic testing, autopsy, or
- Death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out (unexplained death).

**Deep-vein thrombosis (DVT) (66)**

Symptomatic DVT was defined as objectively documented deep-vein thrombosis with one of the following findings:

- A new non-compressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography

- An intraluminal filling defect on venography.

**Non-central nervous system (CNS) systemic embolism**

Non-CNS systemic embolism is defined as abrupt vascular insufficiency of an extremity or organ associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms, (e.g., trauma, atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities should be made with caution and requires angiographic demonstration of abrupt arterial occlusion.

### 16.1.2. Primary bleeding event (PBE)

Bleeding events are primarily adjudicated according to the VARC definitions, following the BARC classification (67).

The components of this primary efficacy endpoint are adjudicated according to the latest valve academic research consortium (VARC) definitions available.

| **VARC Bleeding** |
|---|
| **Life-threatening or disabling bleeding**<br>• Fatal bleeding (BARC type 5) OR<br>• Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR<br>• Bleeding causing hypovolaemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR<br>• Overt source of bleeding with drop in hemoglobin > 5 g/dL or whole blood or packed red blood cells (RBCs) transfusion >4 units * (BARC type 3b) |
| **Major bleeding** (BARC type 3a)<br>• Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBCs, or causing hospitalization or permanent injury, or requiring surgery AND<br>• Does not meet the criteria of life-threatening or disabling bleeding |
| **Minor bleeding** (BARC type 2 or 3a, depending on the severity)<br>• Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major |

Bleeding Academic Research Consortium (BARC).
* Given that one unit of packed RBC typically will raise the n by 1 g/dl, an estimate decrease in hemoglobin will be calculated.

**BARC Bleeding Classification**

**Type 0** No Bleeding

**Type 1** Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional.

**Type 2** Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that **does not** fit the criteria for Types 3, 4, or 5, but **does** meet at least one of the following criteria:
1) Requiring non-surgical, medical intervention by a health care professional
2) Leading to hospitalization or increased level of care 3) Prompting evaluation

**Type 3**

Type 3a

- Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed)

Any transfusion with overt bleeding

Type 3b

- Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous inotropes

Type 3c

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal).
  - Subcategories; Confirmed by autopsy or imaging or LP
- Intra-ocular bleed compromising vision

**Type 4 - CABG–related bleeding**

- Perioperative intracranial bleeding within 48 hrs
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period*.
- Chest tube output ≥ 2L within a 24 hour period

If a CABG - related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'not a bleeding event'

**Type 5 - Fatal Bleeding**

Type 5a

- Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Type 5b

- Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes.
If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.
*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin).
†Cell saver products are not counted.
CABG indicates coronary artery bypass graft.

**TIMI Bleeding Criteria (68, 69)**

**Non-CABG related bleeding**

- **Major**
  - Any intracranial bleeding (excluding microhemorrhages < 10mm evident only on gradient-echo MRI)
  - Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5g/dL
  - Fatal bleeding (bleeding that directly results in death within 7 days
- **Minor**
  - Clinically overt (including imaging), resulting in hemoglobin drop of 3 to < 5g/dL
- **Requiring medical attention**
  - Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
  - Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
  - Leading to or prolonging hospitalization
  - Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)
- **Minimal**
  - Any overt bleeding event that does not meet the criteria above

| **ISTH Bleeding Criteria (70)** |
|---|
| **Major bleeding**<br>• Clinically overt bleeding that is associated with:<br>o A fall in hemoglobin of 2 g/dL or more, or<br>o A transfusion of 2 or more units of packed red blood cells or whole blood, or<br>o A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or<br>o A fatal outcome |
| **Non-major clinically relevant bleeding**<br>• Overt bleeding event not meeting the criteria for a major bleeding event but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life. Examples include:<br>o Epistaxis if it lasts for more than 5 minutes, if it is repetitive (i.e., 2 or more episodes of true bleeding, i.e., no spots on a handkerchief, within 24 hours), or leads to an intervention (packing, electrocautery, etc.)<br>o Gingival bleeding if it occurs spontaneously (i.e., unrelated to tooth brushing or eating), or if it lasts for more than 5 minutes<br>o Hematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract<br>o Macroscopic GI hemorrhage: at least 1 episode of melena or hematemesis, if clinically apparent<br>o Rectal blood loss, if more than a few spots<br>o Hemoptysis, if more than a few speckles in the sputum, or<br>o Intramuscular hematoma<br>o Subcutaneous hematoma if the size is larger than 25 $cm^2$ or larger than 100 $cm^2$ if provoked<br>o Multiple source bleeding events<br>**Minimal**<br>• All other overt bleeding episodes not meeting the criteria for major or clinically relevant non-major bleeding. |

## 16.2. Definitions of terms

*This section was modified with Amendment 3. For details, see Section 15.2.*

**Acute kidney injury**

Acute kidney injury is define according to the VARC-2 definitions (29), following the AKIN Classification (71). The timing for diagnosis of AKI is up to 7 days and subjects who experience AKI should have follow-up renal assessments after 7 days until stabilization.

| Acute Kidney Injury (AKIN Classification) | |
|---|---|
| **Stage 1** | Increase in serum creatinine to 150-199 % (1.50-1.99 x increase compared with baseline) OR increase of > 0.3 mg/dl (> 26.4 mmol/l) OR<br>Urine output < 0.5 ml/kg/h for > 6 but < 12h |
| **Stage 2** | Increase in serum creatinine to 200-299% (2.00-2.99 x increase compared with baseline) OR<br>Urine output < 0.5 ml/kg/h for > 12 but < 24h |
| **Stage 3** | Increase in serum creatinine to > 300% (> 3 x increase compared with baseline) OR serum creatinine of > 4.0 mg/dl (> 354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l) OR<br>Urine output < 0.3 ml/kg/h for > 24h OR<br>Anuria for > 12h<br>Patients receiving renal replacement therapy. |

The increase must occur within 48 hours.

### Aortic stenosis (AS)

Aortic stenosis (AS) typically refers to a narrowing, stiffening or obstruction of flow at the level of the native aortic valve. The recently released AHA/ACC heart disease guidelines define the stages for AS (33).

### Child-Pugh Classification of Severity of Liver Disease (72, 73)

Modified Child-Pugh classification of severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy.

| Parameter | Points assigned 1 | 2 | 3 |
|---|---|---|---|
| Ascites | Absent | Slight | Moderate |
| Bilirubin, mg/dL | ≤ 2 | 2-3 | >3 |
| Albumin, g/dL | >3.5 | 2.8-3.5 | <2.8 |
| Prothrombin time | | | |
| - Seconds over control | 1-3 | 4-6 | >6 |
| - INR | <1.8 | 1.8-2.3 | >2.3 |
| Encephalopathy | None | Grade 1-2 | Grade 3-4 |

| Grade | Points |
|---|---|
| A: well-compensated disease | 5-6 |
| B: significant functional compromise | 7-9 |
| C: decompensated disease | 10-15 |

**Moderate renal impairment**

Kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 $m^2$ for ≥ 3 months or with estimated creatinine clearance <50 mL/min. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

**Non-active prostate cancer**

No current or planned diagnostic measures, chemotherapy, surgical treatment or a reduced life expectancy.

**New-onset atrial fibrillation (NOAF) or new-onset atrial flutter (74)**

NOAF or atrial flutter is diagnosed as a common supraventricular arrhythmia that is characterized by an uncoordinated contraction of the atrium. An electrocardiogram (ECG) recording is necessary to diagnose AF or atrial flutter. Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or for at least 30 seconds on a rhythm strip is considered to be either AF or atrial flutter. The therapeutic approach to NOAF (spontaneous conversion, electrical or medical cardioversion, initiation of oral anticoagulation, and rate control), should be considered an AF episode. The diagnosis requires an ECG or rhythm strip and any clinical consequences should be thoroughly documented in the case report form.