CLINICAL STUDY PROTOCOL

EDOXABAN VERSUS STANDARD OF CARE AND THEIR EFFECTS ON CLINICAL OUTCOMES IN PATIENTS HAVING UNDERGONE TRANSCATHETER AORTIC VALVE IMPLANTATION – IN ATRIAL FIBRILLATION

EDOXABAN (DU-176B-C-U4001)

ENVISAGE-TAVI AF

EudraCT NUMBER 2016-003930-26/IND NUMBER 77 254

Sponsor's Protocol Code Number DU-176B-C-U4001

VERSION 4.0 29 JUL 2019

DAIICHI SANKYO

CONFIDENTIALITY STATEMENT

INVESTIGATOR AGREEMENT

Edoxaban versus standard of care and their effects on clinical outcomes in patients having undergone transcatheter aortic valve implantation – in atrial fibrillation

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo Inc. representatives listed below.

PPD	PPD
Print Name	**Signature**
Sr. Medical Director	8/1/2019 | 10:35 AM EDT
Title	**Date (DD MMM YYYY)**

Lead Investigator Approval:

PPD	
Print Name	**Signature**
Director of Cardiovascular Innovation	
Title	**Date (DD MMM YYYY)**
PPD	
Print Name	**Signature**
Clinical Dir. Interventional Cardiology	
Title	**Date (DD MMM YYYY)**

INVESTIGATOR'S SIGNATURE

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines on Good Clinical Practice (International Committee on Harmonisation [ICH] E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

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a. a: Daiichi Sankyo Pharma Development is an unincorporated division of Daiichi Sankyo Inc.
b. b: Daiichi Sankyo Company Limited is the holding company of Daiichi Sankyo, Inc.

PROTOCOL SYNOPSIS

EudraCT:	2016-003930-26
IND Number:	*77 254*
Protocol Number:	DU-176b-C-U4001
Investigational Product:	Edoxaban (DU-176b)
Active Ingredient(s)/INN:	N-(5-Chloropyridin-2-yl)-N′-[(1S,2R,4S)-4-(N,N-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-carboxamido)cyclohexyl]oxamide mono (4-methylbenzenesulfonate) monohydrate/Edoxaban
Study Title:	Edoxaban Versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation – In Atrial Fibrillation
Study Acronym	ENVISAGE-TAVI AF
Study Phase:	Phase 3b
Indication Under Investigation:	Use of Edoxaban in patients with atrial fibrillation (AF) and indication to chronic oral anticoagulant (OAC) medication after transcatheter aortic valve implantation (TAVI)
Study Objectives:	**Co-primary objectives** • To assess the effect of Edoxaban versus Vitamin K antagonist (VKA) on net adverse clinical events (NACE), i.e., the composite of all-cause death, myocardial infarction (MI), ischemic stroke, systemic thromboembolism (SEE), valve thrombosis, and major bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition). • To assess the effect of Edoxaban versus VKA on major bleeding (ISTH definition). **Secondary objectives:** To compare Edoxaban with VKA with regards to the following **efficacy endpoints**: • NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and

major and minor bleeding per Thrombolysis in Myocardial Infarction (TIMI) definitions

- NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (Bleeding Academic Research Consortium [BARC] 3 or 5 definition)
- NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major and moderate bleeding (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO] definition)
- Major Adverse Cardiac Events (MACE), defined as the composite of all-cause death (excluding adjudicated non-cardiac death), MI, or repeat coronary revascularization of the target lesion
- Major Adverse Cardiac and Cerebrovascular Events (MACCE), defined as the composite of all-cause death (excluding adjudicated non-cardiac death), MI, stroke (ischemic, hemorrhagic, or undetermined), or repeat coronary revascularization of the target lesion
- Cardiovascular mortality
- Stroke (ischemic, hemorrhagic, or undetermined)
- Stroke (ischemic)
- Stroke (hemorrhagic)
- Stroke (undetermined)
- Fatal stroke (ischemic, hemorrhagic, or undetermined)
- Non-fatal stroke (ischemic, hemorrhagic, or undetermined)
- Systemic embolic event
- Myocardial infarction
- Valve thrombosis

To compare Edoxaban with VKA with regards to the following **safety endpoints**:

- Bleeding defined as TIMI major or minor, BARC 3 or 5, and GUSTO moderate or severe
- Bleeding defined as ISTH major and Clinically Relevant Non-major (CRNM); TIMI major/minor

bleeds or requiring medical attention; BARC 2, 3, or 5; and GUSTO moderate or severe

- Bleeding defined as ISTH CRNM, TIMI minor or requiring medical attention, BARC 2, and GUSTO moderate
- All bleeding that are not ISTH major, CRNM; TIMI minimal; BARC 1 non-actionable; and GUSTO mild
- Any bleeding
- Intracranial hemorrhage
- Life-threatening bleeding
- Fatal bleeding (fulfilling the ISTH major bleeding definition)
- Non-fatal major bleeding (ISTH definition)
- All-cause mortality
- Cardiovascular mortality
- Safety parameters such as (serious) adverse events (S[AE]), laboratory parameters, electrocardiogram (ECG) and vital signs

Other objectives:

To compare Edoxaban with VKA with regards to the following:

- Number of hospital admissions, defined as ≥ 24 h stay in the hospital, due to cardiovascular causes (post TAVI and non-TAVI procedure related), including but not limited to overall, for bleeding, SEE, venous thrombosis, shock, arrhythmia, cardiac rupture, stroke, aneurysms, stent occlusions, etc.)
    - Note: Hospital admissions due to cardiovascular causes include, but are not limited to the Emergency Department (ED), Intensive Care Unit (ICU), or cardiovascular ward
- Treatment satisfaction as assessed by the Perception Anticoagulant Treatment Questionnaire (PACT-Q)
- Health related quality of life as assessed by the Euro Quality of Life (EQ-5D-5L) Questionnaire
- Optional: Sub-studies not interfering with the main study may be added including such as the assessment

	of biomarkers of hemostasis/coagulation and of cardiovascular risk such as but not limited to whole blood clotting time (WBCT), thromboelastography (TEG), and multiple electrode aggregometry (MEA), high sensitivity-troponin T (Hs-TnT), growth differentiation factor-15 (GDF-15), and cystatin-C.

Study Design:	This is a multinational, multicenter, prospective, randomized, open-label study with blinded evaluation of endpoints (PROBE) parallel group study comparing Edoxaban with VKA in subjects with AF having undergone TAVI. Critical events will be adjudicated by an independent Clinical Events Committee (CEC). An independent Data and Safety Monitoring Board (DSMB) is responsible for monitoring safety during the study.
	
	Following signing of written informed consent, subjects are screened for eligibility and may be randomized from the evening of the day of TAVI to 5* days, i.e., until 23:59 of the 5^{th*} day after the successful TAVI procedure (see inclusion criteria #1 for definition of "successful") and the subject is qualified based on all the protocol-defined inclusion/exclusion criteria. The first dose of OAC should be administered within the 5 days after TAVI (in case of pacemaker deployment within the 7 days after TAVI) but must be administered within 24 hours post randomization, however NO EARLIER than the morning after successful TAVI.
	
	*If subject is waiting on a decision on pacemaker surgery, then can extend to 7 (7th) days
	
	Subjects eligible to participate in the study will be randomized via interactive web/voice response system (IXRS) such that the study will have a 1:1 ratio of subjects in the following study arms:
	
	• **Edoxaban-based regimen:**
	  o Edoxaban 60 mg once-daily or 30 mg once-daily in subjects meeting the dose reduction criteria per locally approved label
	
	• **VKA-based regimen:**
	  o The VKA of choice (any locally approved), dose-adjusted throughout the study to achieve an international normalized ratio (INR) of 2.0 to 3.0 (numbers inclusive)

	[Japan: 1.6 to 2.6 in subjects aged ≥70 (numbers inclusive)]. In addition to the above described oral anticoagulation therapy, antiplatelet management in this study shall follow the scenarios as outlined below: • Subjects having undergone TAVI without other potential indications for antiplatelet therapy (APT) may obtain either no APT or single antiplatelet therapy (SAPT) up to 90 days, i.e., acetylsalicylic acid (ASA) or any $P2Y_{12}$ inhibitor (preferably clopidogrel). • Subjects having undergone TAVI with percutaneous coronary intervention (PCI) either prior to or during the study period may obtain SAPT indefinitely, i.e., any $P2Y_{12}$ inhibitor (preferably clopidogrel) or ASA. Dual anti-platelet therapy (DAPT) is only allowed post stenting for up to 3 months after each PCI during this study. • Subjects having undergone TAVI with other potential indications for oral antiplatelet therapy may obtain either no APT or SAPT, i.e., any $P2Y_{12}$ inhibitor (preferably clopidogrel) or ASA indefinitely. **The type (i.e., the international nonproprietary name, the dose, and the projected last dose of all antiplatelet agents) must be predeclared at randomization. ASA 75-100 mg/day or generic/branded clopidogrel 75 mg/day (chronic therapy following loading dose) are the preferred agents. Type, dose, and (projected) last dose may be changed during the treatment period for documented medical reasons.**
Study Duration:	Subjects will be monitored throughout the entire study period regardless of whether they have or have not experienced an endpoint. Monitoring will be performed with study visits (which can be on-site or at the subject's current place of living, but the monitoring will be conducted by the Investigator or qualified designee) at 3 and 6 months post randomization, then semi-annually, at the end of the treatment period, and at 30 days after the last dose of the study medication (see Table 17.1). After the End of Treatment Visit, subjects will have the option to be followed by telephone contact with the site and/or review of their

	medical records by qualified site personnel until the end of the study (common study end date [CSED]). The enrollment will be stopped no later than at the attainment of a total of 320 subjects experiencing an adjudicated NACE across the combined treatment arms, and the study will continue until the last subjects enrolled will have accomplished the minimum treatment duration of at least 6 months plus their Post-treatment Follow-up Visit.
Study Sites and Locations:	It is planned to enroll approximately 1400 subjects with a 1:1 randomization ratio (Edoxaban: VKA) approximately 200 study sites located in the USA, Canada, Europe (Austria, Belgium, France, Germany, Italy, the Netherlands, Spain, Switzerland, UK and potentially other countries), and Japan. Other countries may also participate.
Planned Sample Size:	The primary endpoint is NACE. In order to determine the sample size, the following assumptions were made: • *Event rate:* Based on published literature and results from the ENGAGE AF-TIMI 48 study, it is assumed that the event rate of the primary efficacy endpoint of NACE in AF-subjects treated post TAVI with VKA would be 14%/year. • *Noninferiority margin*: No data were available for placebo-controlled studies in this subject population. The Executive Committee reviewed all available data including practice changes observed in other areas of cardiology on the basis of clinical studies and the level of statistical certainty they had achieved. Then it made the judgment that a noninferiority margin for hazard ratio 1.38 would be accepted by the medical community for a practice change given the fact that other studies have already supported the use of Edoxaban in subjects warranting anticoagulation and given its related regulatory approval for human use in the participating countries. • *Significance level for statistical testing*: 0.05. • *Observed hazard ratio*: 0.95. With the above assumptions, to demonstrate noninferiority with 80% of power, the study needs to collect at least

320 NACE across the combined study arms. With an anticipated median follow-up time of two years and an annual event rate of 14%, a total of approximately 1400 subjects need to be randomized.

The sample size is event driven. The sample size or the duration of follow-up may require adjustment based on the actual vs. anticipated primary endpoint event and drop-out rates.

Subject Eligibility Criteria: **Inclusion criteria**

Subjects must satisfy all of the following criteria to be included in the study:

1. Successful TAVI via transvascular access routes such as femoral, carotid, axillary, and subclavian arteries. Other access routes need prior approval per majority vote from 3 members of the Executive Committee (both Global Lead Investigators and the Daiichi Sankyo Medical Lead or his/her designee). Success is defined as:
    a. Correct positioning of a single prosthetic heart valve into the proper anatomical location
    b. Presence of all 3 conditions post TAVI
        i. Mean aortic valve gradient <20 mm Hg
        ii. Peak transvalvular velocity <3.0 m/s
        iii. Aortic valve regurgitation of 2 or less
    c. No clinically overt stroke
    d. No uncontrolled bleeding at time of randomization
2. Indication for chronic OAC
    a. Documented pre-existing AF
    b. New onset AF (e.g., > 30 seconds documented by ECG)
3. Provision of signed informed consent
4. Age ≥18 years

Exclusion criteria

Bleeding risks or systemic conditions

1. Conditions with a high risk of bleeding
    - This may include but is not limited to: active peptic ulcer with upper gastrointestinal bleeding within last 90 days prior to randomization, malignancy at high risk of bleeding, major intraspinal or intracerebral vascular abnormalities, recent unresolved brain or spinal injury, or spinal surgery (recent = within the last 90 days prior to randomization), any intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, or clinically relevant vascular aneurysms
2. Other known bleeding diathesis
3. Conditions that make it difficult for the subject to swallow the study medication

Procedure related

4. Serious unresolved periprocedural complications

Medication related

5. Any contraindication to EITHER Edoxaban OR VKA per local label; this includes hypersensitivity to the active ingredient, to any of the excipients, or any of the components of the study medications
6. Concomitant treatment with other antithrombotic agents ASA > 100 mg/day, fibrinolytic therapy, or chronic (> 4 days/week) use of nonsteroidal anti-inflammatory drugs (NSAIDs); however, NSAID patches are permitted
7. Requirement for dual antiplatelet therapy (DAPT) at randomization that will be indicated for more than 3 months beyond the first study dose of OAC
8. Treatment with other investigational (i.e., non-approved) drugs or devices within 30 days before enrollment or planned use of investigational drugs or devices during the study

Concomitant conditions and therapies

9. Clinically overt stroke within the last 90 days before TAVI
10. Any scheduled drug or device-based therapy during the treatment period that would eliminate the need for chronic oral anticoagulation (any other diagnostic or therapeutic procedure that is associated with temporary interruption of OAC is permitted)
11. (*former exclusion criteria 11 is no longer applicable, numbers not adjusted to keep alignment with version 2.0 of the protocol*)
12. Any bail out catheter based on cardiac interventional procedure during the index TAVI (however, during the same session as TAVI (pre or post TAVI) scheduled PCI and angioplasty of the iliac/femoral arteries are permitted)
13. Subjects with mechanical heart valves
14. Mitral valve stenosis Grade III-IV/IV (moderate to severe/severe); however, subjects with moderate mitral valve stenosis may be enrolled into the study
15. Active infective endocarditis
16. Major surgery within 30 days prior to randomization
17. *(former exclusion criteria 17 is no longer applicable, numbers not adjusted to keep alignment with version 2.0 of the protocol*)
18. ST-elevation myocardial infarction within 30 days prior to TAVI until randomization (non-ST-elevation myocardial infarction is no exclusion)
19. End stage renal disease (creatinine clearance < 15 mL/min or dialysis) at randomization
20. Severe hepatic impairment or hepatic disease associated with coagulopathy (e.g., acute/chronic active hepatitis or cirrhosis, Child Pugh B, C)
21. Uncontrolled severe hypertension documented by repeated BP of ≥170/100 mmHg, despite medical intervention
22. Respiratory failure requiring mechanical ventilation at time of randomization

23. Critically ill or hemodynamically unstable subjects at the time of randomization, (i.e., cardiogenic shock, acute heart failure, including the requirement for pharmacologic treatment or mechanical support to assist circulation)
24. Active malignancy (requiring chemotherapy, radiation or surgery at the time of randomization) except for adequately treated non-melanoma skin cancer or other noninvasive or in situ neoplasms (e.g., cervical cancer in situ that has been successfully treated); anti-hormonal therapy is allowed

Other exclusion criteria

25. Any of the following abnormal local laboratory results at the time of randomization:
    a. Platelet count < 50 x10^9/L
    b. Hemoglobin < 8 g/dL (5 mmol/L at randomization, no ongoing bleeding, no blood transfusion of whole blood or red blood cells within 24 hours); however, for subjects with a history of hemoglobin of no less than 7.5 g/dL while taking chronic OAC, the exclusion will be based on hemoglobin of < 7.5 g/dL
26. Female subjects of childbearing potential without using highly effective methods of contraception (i.e., a method of contraception with a failure rate < 1 % during the course of the study, including the follow up period). A female of childbearing potential is defined as one who has not been postmenopausal for at least one year, or has not been surgically sterilized, or has not had a hysterectomy at least three months prior to the start of this study [Visit 1]). Females taking oral contraceptives should have been on that therapy for at least three months. Highly effective methods of contraception includes combined (estrogen and progestogen containing) oral, intravaginal or transdermal hormonal contraception associated with inhibition of ovulation; progestogen-only oral, injectable or implantable hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS);

	bilateral tubal occlusion; vasectomized partner; along with barrier methods of contraception (male condom, female condom, cervical cap, diaphragm, contraceptive sponge) 27. Pregnant or breast-feeding subjects 28. Assessment by the Investigator that the subject is not likely to comply with the study procedures or will complete follow-up 29. Current participation in another clinical study (unless the registry DOES NOT interfere with the evaluation of ENVISAGE-TAVI-AF as per this protocol. Before including such a subject, the Investigator shall discuss the situation with the Daiichi Medical Lead or his/her designee) 30. Previous randomization in this study 31. Drug or alcohol dependence within the past 12 months prior to randomization as judged by the Investigator 32. Life expectancy less than 6 months beyond the targeted last visit 33. Subjects with antiphospholipid syndrome who are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies) with thrombosis
Dosage Form, Dose and Route of Administration:	Edoxaban: 60 mg and 30 mg film-coated tablets for once-daily oral use, and 15 mg film-coated tablets for transitioning at end of treatment will be provided by the Sponsor. Dosing must follow the locally approved label. VKA: Oral VKA tablets as selected and provided by the site or prescribed by treating physician and used in accordance with the local label to obtain an INR of 2.0 to 3.0 (numbers inclusive) [Japan: 1.6 to 2.6 in subjects aged ≥70 (numbers inclusive)]. It is the Investigator's responsibility throughout the study to collect INR as per medical needs, preferably monthly. The Investigator will monitor the INR and adjust the VKA dose to maintain the INR within target (2.0 to 3.0 (numbers inclusive) [Japan: 1.6 to 2.6 in subjects aged ≥70 (numbers inclusive)]), unless performed by the subject's treating physician. The Investigator will record any changes in VKA dosage within the electronic case report form (eCRF).

	$P2Y_{12}$ antagonist: Clopidogrel (generic or branded) 75 mg, commercially/locally available tablets for once-daily oral use will be provided by the site. Acetylsalicylic acid (ASA): 75-100 mg for once-daily oral use will be provided by the site. Note: Sponsor supplies sites with only Edoxaban study medication: Edoxaban 60 mg and 30 mg film-coated tablets for once-daily oral use, and 15 mg film-coated tablets for transitioning at end of treatment. Sites or treating physicians will provide or prescribe: VKA, clopidogrel, and ASA as per local standard of care and as specified in the protocol. Please refer to the locally approved label for the summary of product characteristics (SmPC) of each study drug.
Study Endpoints:	**Primary efficacy endpoint:** • NACE, i.e., the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (ISTH definition) **Primary safety endpoint:** • Major bleeding (ISTH definition) **Secondary efficacy endpoints:** • NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (TIMI definition) • NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding ([BARC 3 or 5 definition) • NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major and moderate bleeding (GUSTO definition) • Major Adverse Cardiac Events (MACE), defined as the composite of all-cause death (excluding adjudicated non-cardiac death), MI, or repeat coronary revascularization of the target lesion • Major Adverse Cardiac and Cerebrovascular Events (MACCE), defined as the composite of all-cause death (excluding adjudicated non-cardiac death), MI, stroke (ischemic, hemorrhagic, or undetermined), or repeat coronary revascularization of the target lesion

- Cardiovascular mortality
- Stroke (ischemic, hemorrhagic, or undetermined)
- Stroke (ischemic)
- Stroke (hemorrhagic)
- Stroke (undetermined)
- Fatal stroke (ischemic, hemorrhagic, or undetermined)
- Non-fatal stroke (ischemic, hemorrhagic, or undetermined)
- SEE
- Myocardial Infarction
- Valve thrombosis

Secondary safety endpoints:

- Bleeding defined as TIMI major or minor, BARC 3 or 5, and GUSTO moderate or severe)
- Bleeding defined as ISTH major and CRNM, TIMI major/minor bleeds or requiring medical attention, BARC 2, 3 or 5, and GUSTO moderate or severe
- Bleeding defined as ISTH CRNM, TIMI minor or requiring medical attention, BARC 2, and GUSTO moderate
- All bleeding that are not ISTH major, CRNM; TIMI minimal; BARC 1 non-actionable; and GUSTO mild
- Any bleeding
- Intracranial hemorrhage
- Life-threatening bleeding
- Fatal bleeding (fulfilling the ISTH major bleeding definition)
- Non-fatal major bleeding (ISTH definition)
- All-cause mortality
- Cardiovascular mortality
- Safety parameters such as (serious) adverse events, laboratory parameters, ECG and vital signs

	Other endpoints: • Number of hospital admissions, defined as ≥ 24 h stay in the hospital, due to cardiovascular causes (post TAVI and non-TAVI procedure related), including for bleeding, SEE, venous thrombosis, shock, arrhythmia, cardiac rupture, stroke, aneurysms, stent occlusions, etc.). o Hospital admissions due to cardiovascular causes include, but are not limited to the Emergency Department (ED), Intensive Care Unit (ICU), and cardiovascular ward. • Treatment satisfaction as assessed by the Perception Anticoagulant Treatment Questionnaire (PACT-Q) • Health related quality of life as assessed by the EuroQoL (EQ-5D-5L) Questionnaire • Optional: Sub-studies not interfering with the main study may be added including such as the assessment of biomarkers of hemostasis such as but not limited to markers of coagulation and aggregation (sub study), WBCT, TEG, and MEA)], or of cardiovascular and overall prognosis.
Statistical Analyses:	**Four analysis sets are defined:** • The *Intention-to-treat (ITT) analysis set* consists of all randomized subjects irrespective of whether they received a single dose of study Edoxaban or VKA or not. • The *modified Intention-to-treat (mITT) analysis set* consists of all randomized subjects who received at least one dose of study Edoxaban or study VKA according to IXRS assignment. • The *Per Protocol (PP) analysis set* consists of all randomized subjects who received at least one dose of the study regimen according to IXRS assignment and do not have any of the following major protocol violations (for more details, see Section 11.1.3): - A major violation of the inclusion criteria - An unequivocal violation of the exclusion criteria • The *Safety analysis set* (SAF) consists of all randomized subjects who received at least one dose of the study Edoxaban or study VKA according to IXRS assignment.

Definition of terms:

'Overall Study Period': This period is defined as the time from the reference date* up to an estimated Month 36 /end of treatment (EOT) (Visit 8).

'Overall Study Period + 30 days': This period is defined as the time from the reference date* and time of randomization up to an estimated Month 36 /EOT (Visit 8) + 30 days, i.e., to Month 37 (post treatment follow-up visit).

'Initial dose to Final Dose + 30 days': This period is defined as the time period between the date and time of initial dose of study Edoxaban or study VKA and the date and time of final dose of study Edoxaban or study VKA plus 30 days, including study regimen interruptions.

(*) When using the ITT analysis set, the reference date is the date/time of randomization; otherwise, the reference date is the date of first intake of study Edoxaban or study VKA.

Planned Analyses:

There are 4 primary hypotheses that will be tested in hierarchical

order:

- Hypothesis (1):
  - The Edoxaban-based regimen is noninferior to the VKA-based regimen with regards to NACE.
- Hypothesis (2):
  - The Edoxaban-based regimen is noninferior to the VKA-based regimen with regards to major bleeding (ISTH definition).
- Hypothesis (3):
  - The Edoxaban-based regimen is superior to the VKA-based regimen with regards to major bleeding (ISTH definition).
- Hypothesis (4):
  - The Edoxaban-based regimen is superior to the VKA-based regimen with regards to NACE.

The analysis sets and analysis periods to be used for the main analyses related to these four hypotheses are presented below:

Hypothesis	Endpoint	Primary Analysis Set	Primary Analysis Period
(1)	NACE	ITT	Overall study period
(2)	Major bleeding (ISTH def)	ITT	Overall study period
(3)	Major bleeding (ISTH def)	ITT	Overall study period
(4)	NACE	ITT	Overall study period

To control the type-I error rate, these four hypotheses will be tested in a hierarchical manner:

- Step (1): The Edoxaban-based regimen will be considered noninferior to the VKA-based regimen with regards to NACE, if the upper boundary of the two-sided 95% CI for hazard ratio (HR) falls below 1.38. If it is significant, then go to Step (2), otherwise stop here.
- Step (2): The Edoxaban-based regimen will be considered noninferior to the VKA-based regimen with regards to major bleeding (ISTH def.), if the upper boundary of the two-sided 95% confidence interval (CI) for HR falls below 1.38. If it is significant, then go to Step (3), otherwise stop here.
- Step (3): The Edoxaban-based regimen will be considered superior to the VKA-based regimen with regards to major bleeding (ISTH def.), if the upper boundary of the two-sided 95% CI for HR falls below 1.00. If it is significant, then go to Step (4), otherwise stop here.
- Step (4): The Edoxaban-based regimen will be considered superior to the VKA-based regimen with regards to NACE, if the upper boundary of the two-sided 95% CI for HR falls below 1.00.

For each of the primary and secondary adjudicated endpoints, appropriate summary statistics (e.g., event rate) including 95% CI will be provided.

For each of the adjudicated endpoints, the time from reference date to the first occurrence of an event (based on CEC adjudication), is analyzed using a Cox proportional hazard model with treatment regimen as a factor and all the stratification factors from the randomization (IXRS) as covariates, (dose adjustment [yes, no], to provide point estimates and 95% CI for the HR). Depending on the analysis period used in the statistical analysis, subjects without an occurrence of an event will be censored at the last date of the analysis period or at the last date of known outcomes status. The latter is determined an individual basis for subjects with incomplete follow-up.

To evaluate the robustness of the primary analysis, the analysis will be repeated using the mITT and PP analysis set. In addition, the statistical results based on the following analysis periods: 'initial dose to final dose + 30 days' and 'overall study period + 30 days' will be presented but should be interpreted in a more descriptive way.

For time to first event analyses, cumulative event rates over time are summarized using the Kaplan-Meier method as appropriate.

The main analyses for all secondary efficacy and safety endpoints will be based on first occurrence of an (adjudicated) endpoint during the 'overall study period' for all subjects belonging to the ITT analysis set and applying the aforementioned statistical method.

There will be no formal statistical testing for secondary or other exploratory endpoints. Hazard ratios, CI, and p-values are provided but should be interpreted in a purely descriptive exploratory manner.

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LIST OF ABBREVIATIONS

ACRONYM	DEFINITION
AE	Adverse Event
AF	Atrial fibrillation
ALT	Alanine transaminase
APT	Antiplatelet therapy
ASA	Acetylsalicylic acid (aspirin)
AST	Aspartate transaminase
BARC	Bleeding Academic Research Consortium
CBC	Complete blood count
CEC	Clinical events committee
CrCL	Creatinine clearance
CRF	Case Report Form
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
DAPT	Dual antiplatelet therapy
DSMB	Data safety monitoring board
EC	Executive Committee (unless used as part of a European Commission Directive)
ECG	Electrocardiogram
ED	Emergency Department
EOT	End of treatment
EQ-5D-5L	EuroQuality of Life (EQ-5D-5L) Questionnaire
EtC	Ethics Committee
GCP	Good Clinical Practice
GDF-15	Growth differentiation factor-15
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
Hb	Hemoglobin
HEOR	Health economics and outcomes research
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
Hs-TnT	High sensitivity troponin T
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICU	Emergency Care Unit
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional review board
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention-to-treat
IXRS	Interactive web/voice response system
MEA	Multiple electrode aggregometry

ACRONYM	DEFINITION
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified intention to treat
MLBCs	Major late bleeding complications
NACE	Net adverse clinical events
NSAID	Nonsteroidal anti-inflammatory drug
OAC	Oral anticoagulant(s)
OAP	Oral antiplatelet
PACT-Q	Perception of Anticoagulant Treatment Questionnaire
PCI	Percutaneous coronary intervention
P-gp	P-glycoprotein
PP	Per protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAPT	Single antiplatelet therapy
SEE	Systemic embolic event
SmPC	Summary of product characteristics
SOP	Standard operating procedures
STS	Society of Thoracic Surgeons
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAVI	Transcatheter aortic valve implantation
TEAE	Treatment-emergent adverse event
TEE	Transesophageal echocardiography or transesophageal echocardiogram
TEG	Thromboelastography
TIMI	Thrombolysis in Myocardial Infarction
TTE	Transthoracic echocardiography or transthoracic echocardiogram
ULN	Upper limit of normal
VKA	Vitamin K antagonist
WBCT	Whole blood clotting time
WHO	World Health Organization

DEFINITIONS SPECIFIC TO THIS PROTOCOL

Term	Definition for this protocol
Discontinuation	Permanent stoppage of study medication. The subject will not be allowed to restart study medication and should follow the transition procedures outlined in Section 5.2.1.1.2 or Section 5.2.1.2.2.
Interruption	A temporary stoppage of study medication. The subject is allowed to restart the study medication at the discretion of the Investigator.
End of TAVI	The clock for randomization starts with the removal of the sheath with hemostasis
End of Study	As an event driven study, enrollment will be stopped no later than at the attainment of a total of 320 subjects experiencing an adjudicated NACE across the combined treatment arms, and, the study will continue until the last subjects enrolled will have accomplished the minimum treatment duration of at least 6 months plus their Post-treatment Follow-up Visit. This Visit by the last subject enrolled will be defined as theend of the study (or common study end date [CSED].
Major bleeding	Major bleeding is considered to include life-threatening and fatal bleeding.
Study drugs	Any study medication or prescribed oral antiplatelet (OAP) co-administered medication is defined within this protocol as a study drug.
Study medication	The primary medications within this study are Edoxaban and VKA, referred to as study medications. The OAP co-administered medications ($P12Y_2$ inhibitors or ASA) for the purpose of this protocol are NOT referred to as study medications; however, they are included within the term study drugs (see above).
Valve Thrombosis	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 subject whose cause of death was not valve-related should not be reported as valve thrombosis.

1. INTRODUCTION

1.1. Background

Degenerative aortic valve stenosis is the second most common valvular disorder in Europe and in the United States.[1] Its pathogenesis involves chronic valvular tissue inflammation, lipoprotein deposition, osteoblast activation, and extracellular calcifications.[2] Transcatheter aortic valve implantation (TAVI) is a life-saving procedure for patients (est. 48,000 completed in 2014 EU/US)[1,2] with severe aortic stenosis and high, or prohibitive risk for surgery.[3,4] The use of TAVI for the treatment of aortic insufficiency/aortic valve regurgitation has also provided efficacious clinical outcomes.[5,6] The safety and effectiveness of TAVI compared with surgical aortic valve replacement has been demonstrated in clinical randomized trials using both of the two most commonly used TAVI devices, the balloon-expandable Edwards Sapien / SAPIEN XT valve (Edwards Sapien, CA) and the Medtronic Core Valve Revalving System (Medtronic Inc., CA) (4-6).[4,7,8]

Bleeding complications and cerebrovascular events following TAVI are a matter of concern. As compared to percutaneous coronary interventions (PCI), this risk is at least 10-fold higher for TAVI.[9] Patients undergoing TAVI are elder, frail, and at high risk for both stroke (high CHA_2DS_2-VASc score or $CHADS_2$) and bleeding (high HAS-BLEED Score) though at present, studies are underway, that compare the outcome of TAVI versus surgical valve replacement in patients of less overall risk.[10] This risk increases exponentially in patients with atrial fibrillation or other indications to chronic anticoagulation therapy. Balancing the risk of both bleeding and thrombotic events in this population is challenging. Moreover, optimal antithrombotic therapy after TAVI is still unknown. Cerebral imaging studies have shown a very high incidence of new ischemic lesions after TAVI, irrespective of the device or access-site used. The highest risk for embolic cerebrovascular events occurs within 3-6 months after valve implantation. Furthermore, new-onset atrial fibrillation may account for many episodes of stroke at distance from the TAVI procedure. Bleeding complications are associated with significant morbidity and mortality after TAVI. However, not all bleeding complications are mechanical in origin. Many patients require blood transfusions after TAVI despite the absence of an obvious source of bleeding. Moreover, in patients with indication to anticoagulation, VKA exposes such patients to an excessive risk for bleeding. Edoxaban is an oral, reversible, direct factor Xa inhibitor with a linear and predictable pharmacokinetic profile. In the ENGAGE AF-TIMI 48 study both the higher-dose Edoxaban regimen (60 mg) and lower-dose Edoxaban regimen (30 mg) demonstrated to be noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes in a study of 21 105 patients with moderate-to-high risk atrial fibrillation. Therefore, the use of a direct factor Xa inhibitor such as Edoxaban in patients undergoing TAVI may be an attractive option in order to prevent thromboembolic and bleeding events.

Periprocedural access-site bleeding after TAVI is common and is associated with a significant impact on morbidity and mortality. Given the advanced age and the presence

of multiple comorbidities including atrial fibrillation (AF) or coronary artery disease among the currently treated TAVI population, such patients are at higher risk of late (> 30 days) bleeding. Généreux et al. in a pooled analysis from the PARTNER trials and registries characterized the incidence, impact, and predictors of late bleeding following TAVI.[11] Among 2401 patients who underwent TAVI and survived to 30 days, major late bleeding complications (MLBCs) occurred in 142 (5.9%) at a median time of 132 days. The most common causes of MLBCs were gastrointestinal (40.8%) and neurological (15.5%) bleedings. Predictors of MLBCs were atrial fibrillation, left ventricular mass, moderate to severe paravalvular leak and baseline hemoglobin. The MLBCs occurring between 30 days and 1 year were associated with significantly higher rates of death, cardiac death, major stroke, renal failure and rehospitalization. The MLBC was a strong independent predictor of mortality between 30 days and 1 year. The presence of AF, especially when MLBCs occurred, was associated with a poor prognosis and high rate of mortality.

Currently, dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and clopidogrel for 3 to 6 months is an empirical strategy widely accepted for patients undergoing TAVI.[12] However, a randomized single-center study could not find any benefit in patients treated with DAPT for 3 months post TAVI with regards to the risk of cerebrovascular events or major adverse cardiac events compared to ASA monotherapy.[13] Thus, to date the optimal strategy and in particular pharmacological intervention for reducing the risk of cerebrovascular events post TAVI is unknown.

Antithrombotic treatment is believed to be a cornerstone for the prevention of ischemic cerebrovascular accidents during and post TAVI. Current recommendations for antithrombotic agents and strategies for TAVI are not based on large controlled randomized studies.[12,13,14,15,16,17] There is an unmet need for improved antithrombotic therapies and strategies given the fact that the incidence of major stroke has not declined significantly overtime. In PARTNER, heparin was used for procedural anticoagulation (5000 bolus loading dose) with a target of activated clotting time >250 s, whereas guidelines recommend a target time of 300 s. Similarly, dual antiplatelet therapy (loading dose, maintenance dose, duration) after TAVI has not been explicitly defined. PARTNER recommendation was 75-100 mg of daily aspirin, a 300 mg clopidogrel loading dose and 75 mg once-daily for 6 months following TAVI.[14,15] However clopidogrel duration or loading dose are not specifically defined in guidelines, and lately the general usefulness of clopidogrel on top of aspirin in TAVI patients has been questioned.[13,16] In two studies comparing DAPT to single-antiplatelet therapy with either aspirin or clopidogrel, DAPT did not reduce the incidence of new cerebrovascular accidents but was associated with significantly higher rates of major and life-threatening bleeding complications.[13,17] Since it is unclear whether thrombi produced during and after TAVI are of platelet or thrombin based origin, the latter may not favor clopidogrel as an effective agent in these patients.

Controversy also exists for patients with a history of pre-existing atrial fibrillation. No consensus or evidence from trials exist regarding treatment with triple therapy, warfarin with one antiplatelet, or warfarin alone, although American and Canadian guidelines discourage the use of triple therapy.[16,18,19] Triple therapy after TAVI should be avoided in these patients with a high inherent bleeding risk. Furthermore, data show no difference

in stroke rates in single antiplatelet vs. dual antiplatelet therapy, and the combination of one oral anticoagulant with one antiplatelet has recently shown better safety results without excess ischemic events in comparison to triple therapy in AF patients undergoing PCI.[17,20]

1.2. Study Rationale

Edoxaban is a globally approved oral anticoagulant that directly and selectively inhibits factor Xa. Factor Xa initiates the final common pathway of the coagulation cascade inducing the formation of thrombin, which catalyzes additional coagulation-related reactions and promotes platelet activation. Novel anticoagulants such as Edoxaban may have the potential to directly inhibit the TAVI-related thrombogenicity in the early period and at the same time significantly reduce the incidence of bleeding events in patients on standard (Vitamin K antagonist [VKA]) oral anticoagulation.

1.2.1. Dose Rationale

Based on the results of the ENGAGE AF-TIMI 48[21] and Hokusai[22] studies, an Edoxaban dose that is considered as safe and effective for patients with AF or venous thromboembolism and is included in the label (prescribing information) has been selected for this trial. Edoxaban has not been evaluated in patients with AF undergoing TAVI but no additional evidence exists suggesting further dose adaptation.

The doses selected for VKA are those that have been found to be effective in patients with AF.

1.3. Risks and Benefits for Study Subjects

Subjects with AF undergoing PCI with stent placement require the use of oral anticoagulants (OACs) with single or dual antiplatelet therapy (i.e., a $P2Y_{12}$ antagonist and acetylsalicylic acid) to reduce the risk of stroke, systemic embolic event (SEE), stent thrombosis and other myocardial ischemic events, and related cardiovascular morbidity and mortality. Whereas the concomitant use of OACs with antiplatelet agents reduces the risk of thromboembolic events, such therapy also increases the risk of bleeding. Furthermore, the combination of a $P2Y_{12}$ antagonist with aspirin given without OACs is less effective than OACs alone in preventing stroke and SEE in patients with AF.

The risks of Edoxaban in patients undergoing TAVI are not known. For a summary of known risks for Edoxaban and VKA refer to their locally approved label.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Co-Primary Objectives

- To assess the effect of Edoxaban versus Vitamin K antagonist (VKA) on net adverse clinical events (NACE), i.e., the composite of all-cause death, myocardial infarction (MI), ischemic stroke, SEE, valve thrombosis, and major bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition).
- To assess the effect of Edoxaban versus VKA on major bleeding (ISTH definition).

2.1.2. Secondary Objectives

To compare Edoxaban with VKA with regards to the following **efficacy endpoints**:

- NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major and minor bleeding per Thrombolysis in Myocardial Infarction (TIMI) definitions
- NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (Bleeding Academic Research Consortium [BARC] 3 or 5 definition)
- NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major and moderate bleeding (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries [GUSTO] definition)
- Major Adverse Cardiac Events (MACE), defined as the composite of all-cause death (excluding adjudicated non-cardiac death), MI, or repeat coronary revascularization of the target lesion
- Major Adverse Cardiac and Cerebrovascular Events (MACCE), defined as the composite of all-cause death (excluding adjudicated non-cardiac death), MI, stroke (ischemic, hemorrhagic, or undetermined), or repeat coronary revascularization of the target lesion
- Cardiovascular mortality
- Stroke (ischemic, hemorrhagic, or undetermined)
- Stroke (ischemic)
- Stroke (hemorrhagic)
- Stroke (undetermined)
- Fatal stroke (ischemic, hemorrhagic, or undetermined)
- Non-fatal stroke (ischemic, hemorrhagic, or undetermined)

- SEE
- Myocardial Infarction
- Valve thrombosis

To compare Edoxaban with VKA with regards to the following **safety endpoints**:

- Bleeding defined as TIMI major or minor, BARC 3 or 5, and GUSTO moderate or severe
- Bleeding defined as ISTH major and Clinically Relevant Non-Major (CRNM); TIMI major/minor bleeds or requiring medical attention; BARC 2, 3, or 5; and GUSTO moderate or severe
- Bleeding defined as ISTH CRNM, TIMI minor or requiring medical attention, BARC 2, and GUSTO moderate
- All bleeding that are not ISTH major, CRNM; TIMI minimal; BARC 1 non-actionable; and GUSTO mild
- Any bleeding
- Intracranial hemorrhage
- Life-threatening bleeding
- Fatal bleeding (fulfilling the ISTH major bleeding definition)
- Non-fatal major bleeding (ISTH definition)
- All-cause mortality
- Cardiovascular mortality
- Safety parameters such as (serious) adverse events ([S]AEs), laboratory parameters, electrocardiogram (ECG), and vital signs

2.1.3. Other objectives:

To compare Edoxaban with VKA with regards to the following:

- Number of hospital admissions, defined as ≥ 24 h stay in the hospital, due to cardiovascular causes (post TAVI and non-TAVI procedure related), including but not limited to overall, for bleeding, SEE, venous thrombosis, shock, arrhythmia, cardiac rupture, stroke, aneurysms, stent occlusions, etc.
    - Hospital admissions due to cardiovascular causes include, but are not limited to the Emergency Department (ED), Intensive Care Unit (ICU), and cardiovascular ward.
- Treatment satisfaction as assessed by the Perception Anticoagulant Treatment Questionnaire (PACT-Q)
- Health related quality of life as assessed by the Euro Quality of Life (EQ-5D-5L) Questionnaire

- Optional: Sub-studies not interfering with the main study may be added including such as the assessment of biomarkers of hemostasis/coagulation and of cardiovascular risk such as but not limited to whole blood clotting time (WBCT), thromboelastography (TEG), and multiple electrode aggregometry (MEA), high sensitivity-troponin T (Hs-TnT), growth differentiation factor-15 (GDF-15), cystatin-C.

2.2. Study Hypothesis

There are 4 primary hypotheses that will be tested in hierarchical order:

- Hypothesis (1):
  - The Edoxaban-based regimen is noninferior to the VKA-based regimen with regards to NACE.
- Hypothesis (2):
  - The Edoxaban-based regimen is noninferior to the VKA-based regimen with regards to major bleeding (ISTH definition).
- Hypothesis (3):
  - The Edoxaban-based regimen is superior to the VKA-based regimen with regards to major bleeding (ISTH definition).
- Hypothesis (4):
  - The Edoxaban-based regimen is superior to the VKA-based regimen with regards to NACE.

3. STUDY DESIGN

3.1. Overall Design

This is a multinational, multicenter, prospective, randomized, open-label study with blinded evaluation of endpoints (PROBE) parallel group study comparing Edoxaban with VKA in subjects with AF having undergone TAVI. Critical events will be adjudicated by an independent Clinical Events Committee (CEC). An independent Data and Safety Monitoring Board (DSMB) is responsible for monitoring safety during the study.

Following signing of written informed consent, subjects are screened for eligibility and may be randomized the evening of the day of TAVI to 5* days, i.e., until 23:59 of the 5th* day after the successful TAVI (see inclusion criteria #1 for definition of "successful") and the subject is qualified based on all the protocol defined inclusion/exclusion criteria. The first dose of OAC should be administered within the 5 days after TAVI (in case of pacemaker deployment within the 7 days after TAVI) but must be administered within 24 hours post randomization; however, NO EARLIER than the morning after successful TAVI.

*If subject is waiting on a decision on pacemaker surgery, then can extend to 7 (7th) days

- Subjects eligible to participate in the study will be randomized via interactive web/voice response system (IXRS) such that the study will have a 1:1 ratio of subjects in the following study arms (Figure 3.1). Edoxaban 60 mg once-daily or 30 mg once-daily in subjects meeting dose reduction criteria according to the locally approved label.

- **Edoxaban-based regimen:**
  - Edoxaban 60 mg once-daily or 30 mg once-daily in subjects meeting the dose reduction criteria per the locally approved label.
- **VKA-based regimen:**
  - The VKA of choice (any locally approved), dose-adjusted throughout the study to achieve an international normalized ratio (INR) of 2.0 to 3.0 (numbers inclusive) [Japan: 1.6 to 2.6 in subjects aged ≥70 (numbers inclusive)].

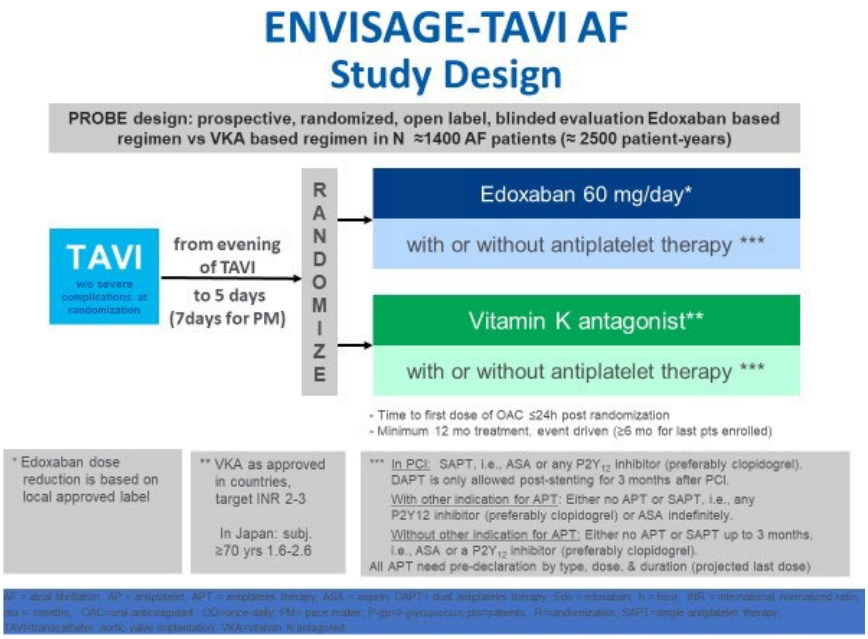
In addition to the above described oral anticoagulation therapy, antiplatelet management in this study shall follow the scenarios as outlined below:

- Subjects having undergone TAVI without other potential indications for antiplatelet therapy (APT) may obtain either no APT or single APT (SAPT) up to 90 days; i.e., ASA or $P2Y_{12}$ inhibitor (preferably clopidogrel).
- Subjects having undergone TAVI with PCI either prior to or during the study period may obtain SAPT indefinitely, i.e., any P2Y12 inhibitor (preferably clopidogrel) or ASA. DAPT is only allowed post stenting for up to 3 months after PCI.

- Subjects having undergone TAVI with other potential indications for oral antiplatelet therapy may obtain either no APT or SAPT, i.e., any $P2Y_{12}$ inhibitor (preferably clopidogrel) or ASA indefinitely.

The type (i.e., the international nonproprietary name, the dose, and the projected last dose of all antiplatelet agents) must be predeclared at randomization. ASA 75-100 mg/day or generic/branded clopidogrel 75 mg/day (chronic therapy following loading dose) are the preferred agents. Type, dose, and (projected) last dose may be changed during the treatment period for documented medical reasons.

Figure 3.1: ENVISAGE-TAVI AF Study Design



*If subject is waiting on a decision on pacemaker surgery, then can extend randomization to 7 (7th) days
NOTE: While it is required to administer the first dose of OAC within 24 h post randomization, this dose is NOT to be administered earlier than the morning after successful TAVI.

3.2. Discussion of Study Design

This study is designed to statistically compare net adverse clinical events of an Edoxaban-based antithrombotic regimen with a VKA-based antithrombotic regimen in non-valvular AF subjects after successful TAVI. At present (2017) there are only limited data and no consensus among experts on how to best treat subject with non-valvular AF following successful TAVI procedures. Hence, medical societies differ in their treatment recommendations as well.[12,13,15,16,17] The current understanding is that antithrombotic therapy is needed using antiplatelet agents for three months and lifelong oral anticoagulants in AF subjects. However, there is a debate on the best timing of the use of antiplatelet agents and oral anticoagulants in such a setting. The situation becomes even more complex in patients with non-valvular AF who either received a stent within the last few months before TAVI or will be subject to stenting after aortic valve replacement as stenting triggers oral antiplatelet therapy for up to 12 months. This scenario applies to at

least 25-34% of the TAVI patients.[23,24,25] Though single antiplatelet therapy is the preferred strategy in the majority of these cases, dual antiplatelet therapy may be warranted for a shorter period of time in patients at high risk for stent thrombosis.

The design of ENVISAGE-TAVI AF accounts for all of these options.

4. STUDY POPULATION

Subjects must sign and date the informed consent form provided by the study center before any study-specific qualification procedures are conducted. While successful TAVI is a required inclusion criterion, the TAVI procedure is not part of this study; however, information derived from the procedure will be documented and used for analysis of this study.

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

1. Successful TAVI via transvascular access routes such as the femoral, carotid, axillary, and subclavian arteries. Other access routes need prior approval per a majority vote from 3 members of the Executive Committee (both Global Lead Investigators and the Daiichi Sankyo Medical Lead or his/her designee). Success is defined as:
    a. Correct positioning of a single prosthetic heart valve into the proper anatomical location
    b. Presence of all 3 conditions post TAVI
        i. Mean aortic valve gradient <20 mmHg
        ii. Peak transvalvular velocity <3.0 m/s
        iii. Aortic valve regurgitation of 2 or less
    c. No clinically overt stroke
    d. No uncontrolled bleeding at time of randomization
2. Indication for chronic OAC
    a) Documented pre-existing AF
    b) New onset AF (e.g., > 30 seconds documented by ECG)
3. Provision of signed informed consent
4. Age ≥18 years

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

4.2.1. Bleeding risks or systemic conditions

1. Conditions with a high risk of bleeding
    - This may include but is not limited to: active peptic ulcer with upper gastrointestinal bleeding within last 90 days prior to randomization, malignancy at high risk of bleeding, major intraspinal or intracerebral vascular abnormalities, recent unresolved brain or spinal injury, or spinal surgery (recent = within the last 90 days prior to randomization), any

intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, or clinically relevant vascular aneurysms

2. Other known bleeding diatheses
3. Conditions that make it difficult for the subject to swallow the study medication

4.2.2. Procedure related

4. Serious unresolved periprocedural complications

4.2.3. Medication related

5. Any contraindication to EITHER Edoxaban OR VKA per local label; this includes hypersensitivity to the active ingredient, or to any of the excipients, or any of the components of the study medications
6. Concomitant treatment with other antithrombotic agents, ASA > 100 mg/day, fibrinolytic therapy, or chronic (> 4 days/week) use of nonsteroidal anti-inflammatory drugs (NSAIDs); however, NSAID patches are permitted
7. Requirement for DAPT at randomization that will be indicated for more than 3 months beyond the first study dose of OAC
8. Treatment with other investigational (i.e., non-approved) drugs or devices within 30 days before enrollment or planned use of investigational drugs or devices during the study

4.2.4. Concomitant conditions and therapies

9. Clinically overt stroke within the last 90 days before TAVI
10. Any scheduled drug or device-based therapy during the treatment period that would eliminate the need for chronic oral anticoagulation (any other diagnostic or therapeutic procedure that is associated with temporary interruption of OAC is permitted)
11. (*former exclusion criteria 11 is no longer applicable, numbers not adjusted to keep alignment with version 2.0 of the protocol*)
12. Any bail out catheter based cardiac interventional procedure during the index TAVI (however, during the same session as TAVI (pre or post TAVI) scheduled PCI and angioplasty of the iliac/femoral arteries are permitted)
13. Subjects with mechanical heart valves
14. Mitral valve stenosis Grade III-IV/IV (moderate to severe/severe); however, subjects with moderate mitral valve stenosis may be enrolled into the study
15. Active infective endocarditis
16. Major surgery within 30 days prior to randomization
17. (*former exclusion criteria 17 is no longer applicable, numbers not adjusted to keep alignment with version 2.0 of the protocol*)
18. ST-elevation myocardial infarction within 30 days prior to TAVI until randomization (non-ST-elevation myocardial infarction is no exclusion)

19. End stage renal disease (creatinine clearance [CrCL] < 15 mL/min or dialysis) at randomization
20. Severe hepatic impairment or hepatic disease associated with coagulopathy (e.g., acute/chronic active hepatitis or cirrhosis, Child Pugh B, C)
21. Uncontrolled severe hypertension documented by repeated BP ≥170/100 mmHg, despite medical intervention
22. Respiratory failure requiring mechanical ventilation at time of randomization
23. Critically ill or hemodynamically unstable subjects at the time of randomization, i.e., cardiogenic shock, acute heart failure, including the requirement for pharmacologic treatment or mechanical support to assist circulation
24. Active malignancy (requiring chemotherapy, radiation or surgery at the time of randomization) except for adequately treated non-melanoma skin cancer or other noninvasive or in situ neoplasms (e.g., cervical cancer in situ that has been successfully treated); anti-hormonal therapy is allowed

4.2.5. Other exclusion criteria

25. Any of the following abnormal local laboratory results at the time of randomization:
    - Platelet count < 50 x 10^9/L
    - Hemoglobin < 8 g/dL (5 mmol/L at randomization, no ongoing bleeding, no transfusion of whole blood or red blood cells within 24 hours); however, for subjects with a history of hemoglobin of no less than 7.5 g/dL while under chronic OAC, the exclusion will be based on hemoglobin of <7.5 g/dL
26. Female subjects of childbearing potential without using highly effective methods of contraception (i.e., a method of contraception with a failure rate < 1% during the course of the study, including the follow-up period). A female of childbearing potential is defined as one who has not been postmenopausal for at least one year, or has not been surgically sterilized, or has not had a hysterectomy at least three months prior to the start of this study [Visit 1]). Females taking oral contraceptives should have been on that therapy for at least three months. Highly effective methods of contraception includes combined (estrogen and progestogen containing) oral, intravaginal or transdermal hormonal contraception associated with inhibition of ovulation; progestogen-only oral, injectable or implantable hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; along with barrier methods of contraception (male condom, female condom, cervical cap, diaphragm, contraceptive sponge).
27. Pregnant or breast-feeding subjects
28. Assessment by the Investigator that the subject is not likely to comply with the study procedures or will complete follow-up
29. Current participation in another clinical trial (unless the registry DOES NOT interfere with the evaluation of ENVISAGE-TAVI-AF as per this protocol.

Before including such a subject, the Investigator should discuss the situation with the Daiichi Sankyo Medical Lead or his/her designee)

30. Previous randomization in this study
31. Drug or alcohol dependence within the past 12 months prior to randomization as judged by the Investigator
32. Life expectancy less than 6 months beyond the targeted last visit
33. Subjects with antiphospholipid syndrome who are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies) with thrombosis

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)

Following the signing of written informed consent, subjects are screened for eligibility and may be randomized the evening of the day of TAVI to 5* days, i.e., until 23:59 of the 5^{th*} day after the successful TAVI (see inclusion criteria #1 for definition of "successful") and the subject is qualified based on all the protocol defined inclusion/exclusion criteria. The first dose of OAC should be administered within the 5 days after TAVI (in case of pacemaker deployment within the 7days after TAVI) but must be administered within 24 hours post randomization; however, NO EARLIER than the morning after successful TAVI. Low-dose aspirin treatment (75-100 mg/day) or approved other $P2Y_{12}$ antagonist, preferably clopidogrel (75 mg/day), will be prescribed as per Investigator discretion. This needs to be pre-declared prior to randomization. Treatment duration will be as per the protocol for up to 36 months (with a minimum of 6 months for last subject enrolled) unless the subject reaches a primary endpoint. However, the subject will continue to be followed until the end of the study (i.e., this may be longer than to end of treatment).

*If subject is waiting on a decision on pacemaker surgery, then can extend to 7 (7th) days

Treatment arms include:

- **Treatment arm 1 [Experimental]: Edoxaban** – 60 mg once-daily or 30 mg once-daily in subjects meeting the dose reduction criteria per the locally approved label.
- **Treatment arm 2 [Control]: VKA** – The oral VKA of choice (any locally approved) dose-adjusted throughout the study to obtain an INR of 2.0 to 3.0 (numbers inclusive) [Japan: 1.6 to 2.6 in subjects aged ≥70 (numbers inclusive)].

In addition to the above described oral anticoagulation therapy, antiplatelet management in this study shall follow the scenarios as outlined below:

- Subjects having undergone TAVI without other potential indications for APT may obtain either no APT or SAPT up to 90 days, i.e., ASA or a $P2Y_{12}$ inhibitor (preferably clopidogrel).
- Subjects having undergone TAVI with PCI either prior to or during the study period may obtain SAPT indefinitely, i.e., any $P2Y_{12}$ inhibitor (preferably clopidogrel) or ASA. Dual antiplatelet therapy (DAPT) is only allowed post stenting for up to 3 months after each PCI during the study period.
- Subjects having undergone TAVI with other potential indications for oral antiplatelet therapy may obtain either no APT or SAPT, i.e., any $P2Y_{12}$ inhibitor (preferably clopidogrel) or ASA indefinitely.

The type (i.e., the international nonproprietary name, the dose, and the projected last dose of all antiplatelet agents) must be predeclared at randomization. ASA 75-100 mg/day or generic/branded clopidogrel 75 mg/day (chronic therapy following loading dose) are the preferred agents. Type, dose, and (projected) last dose may be changed during the treatment period for documented medical reasons.

5.1.2. Method of Treatment Allocation

Prior to randomization of a subject, all eligibility criteria must be met and a signed informed consent obtained.

Enrollment and randomization must occur between the evening of the day of TAVI and 5* days, i.e., until 23:59 of the 5th* day provided that the TAVI procedure has been judged as successful (See inclusion criteria #1 for definition of successful TAVI) and the subject is qualified based on all the protocol defined inclusion/exclusion criteria. All sites will be required to maintain a record of all subjects screened for the trial. The reason for screen failure must be documented in the subject's records. Subjects must be randomized without delay and administered their first dose of study medication within 24 hours post randomization; however, NO EARLIER than the morning after successful TAVI. Randomization will be performed using the IXRS system for subjects meeting all eligibility criteria. The directions on how to use the system will be provided in the IXRS Quick Reference Manual. The randomization scheme will be securely stored at the statistical department of the database management center.

*If subject is waiting on a decision on pacemaker surgery, then can extend to 7 (7th) days

Based on this information, the system will assign a unique subject identification number and treatment for that subject. Trial randomization will not be blinded and once subject is assigned to a treatment arm, no treatment cross-over is permitted. Subjects will be randomly assigned in a 1:1 ratio to receive Edoxaban or VKA. The Investigator will pre-declare the type (if any) $P2Y_{12}$ antagonist or ASA treatment and its projected last dose prior to the randomization (pre-declaration, via the IXRS).

The Investigator's knowledge of the treatment must not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

5.1.3. Blinding

This study is open-label.

5.2. Study Drug(s)

5.2.1. Description

The primary medications within this study are Edoxaban and VKA, referred to as study medications. The oral antiplatelet (OAP) co-administered medications for the purpose of this protocol are not referred to as study medications, but are within the term study drugs. The costs of OAP and VKA for this study will be reimbursed.

5.2.1.1. Edoxaban:

60 mg and 30 mg film-coated tablets for once-daily oral use and 15 mg film-coated tablets for transitioning at end of treatment. Dosing must follow the locally approved label.

5.2.1.1.1. Transitioning from Other Anticoagulants to Edoxaban at Randomization

For subjects randomized to the Edoxaban-based regimen that require switching from another anticoagulant the following algorithm should be used. Capture the date and timing of first study dose in the electronic case report form (eCRF).

Table 5.1: Transitioning to Edoxaban at Randomization

Switching to edoxaban		
From	**To**	**Recommendation**
VKA	edoxaban	Discontinue the VKA and start edoxaban when INR is ≤ 2.5.
Other non-VKA OAC drugs • dabigatran • rivaroxaban • apixaban	edoxaban	Discontinue the OAC and start edoxaban at the time of the next OAC dose.
Parenteral anticoagulants	edoxaban	These agents should not be administered simultaneously. Subcutaneous anticoagulant (i.e. LMWH, fondaparinux): discontinue subcutaneous anticoagulant and start edoxaban at the time of the next scheduled subcutaneous anticoagulant dose. Intravenous unfractionated heparin: Discontinue the infusion and start edoxaban 4 hours later.

INR = international normalized ratio; OAC = Oral anticoagulant(s); VKA = vitamin K antagonist

5.2.1.1.2. Transition from Edoxaban at EOT

For subjects randomized to the Edoxaban-based regimen that require switching from Edoxaban to another anticoagulant at the scheduled end of treatment (EOT) (or due to a premature Edoxaban discontinuation) the following algorithm should be used:

Table 5.2: Transitioning from Edoxaban at EOT

Switching from Edoxaban		
From	**To**	**Recommendation**
Edoxaban	VKA	During the transition from Edoxaban to VKA, continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. **Oral option:** • For subjects currently on a 60 mg once-daily dose, administer an Edoxaban dose of 30 mg once-daily together with an appropriate VKA dose. • For subjects currently on a 30 mg dose once-daily (for one or more of the following factors: moderate to severe renal impairment (CrCL = 15 to ≤ 50 mL/min), low body weight, or use with certain

Switching from Edoxaban		
From	**To**	**Recommendation**
		P-gp inhibitors), administer an Edoxaban dose of 15 mg once-daily together with an appropriate VKA dose. Edoxaban 15 mg once-daily is not indicated as monotherapy, as it may result in decreased efficacy. It is only indicated in the process of switching from Edoxaban 30 mg once-daily to VKA, together with an appropriate VKA dose. Subjects should not take a loading dose of VKA in order to promptly achieve a stable INR of 2.0 to 3.0 (numbers inclusive) [Japan: 1.6-2.6 in subjects aged ≥70 (numbers inclusive)]. It is recommended to take into account the maintenance dose of VKA if the subject was previously taking a VKA or to use valid INR driven VKA treatment algorithm, in accordance with local practice. Once an INR ≥ 2.0 is achieved [Japan: ≥1.6 in subjects aged ≥70], Edoxaban should be discontinued. Most subjects (85%) should be able to achieve an INR ≥ 2.0 [Japan: 1.6 in subjects aged ≥70 (numbers inclusive)] within 14 days of concomitant administration of Edoxaban and VKA. After 14 days it is recommended that Edoxaban is discontinued and the VKA continued to be titrated to achieve an INR of 2.0-3.0 (numbers inclusive) [Japan: 1.6-2.6 in subjects aged ≥70 (numbers inclusive)]. It is recommended that during the first 14 days of concomitant therapy the INR is measured at least three times just prior to taking the daily dose of Edoxaban to minimize the influence of Edoxaban on INR measurements. Concomitant Edoxaban and VKA can increase the INR post Edoxaban dose by up to 46%.
		Parenteral option: Discontinue Edoxaban and administer a parenteral anticoagulant and VKA at the time of the next scheduled Edoxaban dose. Once a stable INR of ≥2.0 is achieved [Japan: ≥1.6 in subjects aged ≥70], the parenteral anticoagulant should be discontinued and the VKA continued.
Edoxaban	Other non-VKA OAC drugs	Discontinue Edoxaban and start the non-VKA anticoagulant at the time of the next scheduled dose of Edoxaban.
Edoxaban	Parenteral anticoagulants	These agents should not be administered simultaneously. Discontinue Edoxaban and start the parenteral anticoagulant at the time of the next scheduled dose of Edoxaban.

CrCL = creatinine clearance; INR = international normalized ratio; OAC = Oral anticoagulant(s); P-gp = P-glycoprotein; VKA = vitamin K antagonist

5.2.1.2. VKA

Any oral VKA tablet of choice for use in accordance with the local label to obtain an INR of 2.0 to 3.0 (numbers inclusive) [Japan: 1.6 to 2.6 in subjects aged ≥70 (numbers inclusive)]

It is the responsibility of the Investigator to collect INR at study visits, and in between study visits (preferably monthly), as needed per standard of care, in order to maintain INR within the target range. The Investigator will monitor the INR and adjust the VKA dose to maintain the INR within target (2.0 to 3.0 (numbers inclusive) [Japan: 1.6-2.6 in subjects aged ≥70 (numbers inclusive)]), unless performed by the subject's treating physician. The Investigator will record any changes in VKA dosage within the eCRF.

5.2.1.2.1. Transitioning to Study VKA at Randomization

For subjects randomized to VKA, who require switching from any other anticoagulant i.e., another VKA, other non-VKA OAC, or parenteral anticoagulants, follow the guidance for switching in the locally approved labels of these products. Capture the date and timing of first study dose in eCRF.

Table 5.3: Transitioning to Study VKA at Randomization

Switching to VKA		
From	**To**	**Recommendation**
Vitamin K Antagonist (VKA)	Study VKA	If the INR measured on the day of randomization is: • ≤ 2.5, start study VKA • > 2.5, the Investigator or designee must recheck at a later time; start study VKA when the INR is ≤ 2.5: document the INR value and the date it was measured.
Other non-VKA OAC drugs • dabigatran • rivaroxaban • apixaban	Study VKA	Ascertain adequate anticoagulation until an INR ≥2.0 is reached and then continue with study VKA only. Follow local label of country-selected VKA and label of NOAC being stopped for further guidance.
Parenteral anticoagulants	Study VKA	For subjects not previously on VKA, bridging with parenteral anticoagulation is permissible, but not recommended. For initiation of VKA therapy and related bridging with parenteral anticoagulation, follow locally established guidelines and local approved label (prescribing information) from the VKA manufacturer.

INR = international normalized ratio; NOAC = non- oral anticoagulant(s); OAC = oral anticoagulant(s); VKA = vitamin K antagonist

5.2.1.2.2. Transitioning from Study VKA at EOT

Table 5.4: Transitioning from Study VKA at EOT

Switching from VKA		
From	**To**	**Recommendation**
Study VKA	VKA	When transitioning a subject to post-study VKA, either maintain the subject on the same maintenance dose or adjust the dose of VKA to maintain an INR between 2.0-3.0 and follow the local guidelines for managing patients on VKA therapy.
Study VKA	Other non-VKA OAC drugs	When transitioning a subject to a newer non-VKA oral anticoagulant, switching guidance in the locally approved label of the non-VKA anticoagulant should be followed.

INR = international normalized ratio; OAC = Oral anticoagulant(s); VKA = vitamin K antagonist

5.2.1.3. $P2Y_{12}$ antagonist:

Clopidogrel (generic/branded) 75 mg, commercially/locally available tablets for once-daily oral use is the preferred $P2Y_{12}$ antagonist for this study.

5.2.1.4. Acetylsalicylic acid (ASA):

ASA 75-100 mg once-daily for oral use.

5.2.2. Supply of Medications

Sponsor supplies participating sites with Edoxaban, consisting of 60 mg and 30 mg film-coated tablets. The Sponsor will also supply transition kits containing Edoxaban 30 mg and 15 mg to be used for subjects transitioning from Edoxaban to VKA.

Sites or treating physicians will provide or prescribe VKA, clopidogrel, and ASA as per local standard of care guidelines and as specified in the protocol. Please refer to the locally approved label for the summary of product characteristics (SmPC) of each study medication and co-administered medication.

All dosage adjustments for Edoxaban are implemented through the IXRS system at the time of the subject's study visits. For subjects randomized to Edoxaban treatment, the IXRS system provides the appropriate Edoxaban supply kit number based on the subject's information as provided by the Investigator.

5.2.3. cLabeling and Packaging

Edoxaban (DU-176b) will be supplied as tablets (60 mg and 30 mg strengths) packaged in bottles of 60 tablets in each bottle. Two bottles will be supplied to cover the 3 month treatment periods and 4 bottles for the 6 month treatment periods. Edoxaban (DU-176b) will be supplied as 15 mg tablets for end of treatment transition at end of treatment. The transition supply will consist of Edoxaban 30 mg tablets or 15 mg tablets packaged in bottles of 15 tablets each. Protocol-specific packaging and labeling will be completed following Good Manufacturing Principles (GMP).

Subjects will obtain their standard of care medications (e.g., VKA, clopidogrel, and ASA), excluding Edoxaban, either from the site or via prescription from the hospital or treating physician.

5.2.4. Preparation

There is no special preparation for either Edoxaban tablets or VKA.

5.2.5. Administration

For Edoxaban will be dosed as per IXRS. VKA administration will be based on locally approved label instructions. For subjects on VKA, VKA administration should be at doses that will to obtain/maintain an INR of 2.0 to 3.0 (numbers inclusive) [Japan: 1.6 to 2.6 in subjects aged ≥70 (numbers inclusive)].

5.2.6. Storage

Edoxaban tablets must be stored by the site at 20°to 25°C (68° to 77°F) as measured by a thermometer in a secure, limited access storage area. Temperature measurements will be recorded on a temperature log excluding weekends and holidays.

Excursions from 15°to 30°C (59° to 86°F) are permitted. The Sponsor/contract research organization (CRO) must be contacted in the event of a temperature excursion outside this range.

Other medications must be stored as per labeled storage conditions.

Upon receipt of shipment, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, confirm temperature monitor readings, and sign the Receipt of Shipment Form provided and file the latter in the site binder. The Investigator or designee will contact the IXRS to acknowledge receipt of shipment. In addition, the Investigator or designee shall contact Sponsor/CRO as soon as possible if there is a problem with the shipment and quarantine the shipment until resolution is obtained from the Sponsor.

5.2.7. Edoxaban Accountability

The IXRS will contain a Drug Accountability Module for any medications provided by the Sponsor (i.e., Edoxaban). The Investigator or designee will enter the required information (see IXRS Quick Reference Manual) in the IXRS drug accountability module. In addition, the Investigator or designee shall contact Sponsor as soon as possible if there is a problem with the shipment. A drug accountability record will be provided for Edoxaban. The record must be kept current and should contain the dates and quantities of Edoxaban received, subject's identification number or supply number as applicable, for whom the Edoxaban was dispensed, the date and quantity of Edoxaban dispensed and remaining, as well as the initials of the dispenser.

At the end of the study or as directed, all Edoxaban, including unused, partially used, or empty bottles, will be returned to the Sponsor, a designee, or destroyed at the site according to the site's drug handling and disposition standard operating procedures (SOPs). A copy of these SOPs must be available onsite. The certificate of destruction must be provided to Daiichi Sankyo documenting the drug, the quantity (in tablets), method of destruction, and date of destruction.

If sites are unable to destroy drug, the monitor will make arrangements to return drug to a designated depot for destruction.

Medications provided by the Sponsor will be destroyed (or returned) only after the study monitor has completed an inventory to verify the quantity to be destroyed (or returned). The destruction (or return) of medications provided by the Sponsor must be documented and the documentation filed (and if returned, included in the shipment).

All investigational product inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

5.3. Control Treatment

Sites and or treating physicians will provide or prescribe VKA, clopidogrel, and ASA as per local standard of care guidelines and as specified within the protocol.

5.4. Dose Reductions

Dose reduction for Edoxaban or VKA will be based on the country-specific approved label precautions and recommendations.

5.5. Method of Assessing Treatment Compliance

The first dose of randomized study medication regimen is administered under nursing supervision. Each subject should document missed doses and Investigator captures information in the eCRF.

As per Table 17.1, the Investigator or designee assesses the subject's compliance with the assigned regimen which may include the subject's memory aid; however, dosing compliance will be primarily by:

- Dosing compliance for **Edoxaban** will be assessed by means of tablet/bottle counts remaining or bottles returned. All Edoxaban packaging will be returned at each subject visit; an accounting of tablets will be made and recorded in the eCRF. If zero tablets/bottles returned, ask subject whether any were disposed/thrown away, rather than taken orally, and this information will be recorded in the eCRF.
- Dosing compliance for **VKA** will be assessed by time within the therapeutic range of an INR from 2.0 to 3.0 (numbers inclusive) [Japan: 1.6 to 2.6 in subjects aged ≥70 (numbers inclusive)]. INR values will be entered into the eCRF.
- Dosing compliance to any other co-administered medications, (i.e., **oral antiplatelets)** will also be assessed by following prescriptions and subject interview. The information will be recorded in the eCRF.

All information on compliance with medications will be entered into the eCRF.

5.6. Prior and Concomitant Medications

Pre-specified medications that the subject has taken within 30 days before randomization will be recorded in the "targeted concomitant medications" eCRF. Subjects who were or are being treated with oral and/or parenteral anticoagulants are eligible for the study only if from the time of randomization these drugs can be replaced by another oral anticoagulant. These pre-specified medications taken by the subjects upon entry to the study or at any time during the study are regarded as targeted concomitant medications and must be documented on the appropriate pages of the eCRF. If the subject experiences an endpoint event or an SAE, then information on targeted and non-targeted concomitant medications taken within the past 30 days prior to the SAE through to the resolution of the SAE must be documented on the appropriate eCRF pages. Concomitant therapy will be captured through the subject's Post-treatment Follow-up Visit, or in the

case of an SAE reported between that visit and the end of the study, see previous sentence.

With the exception of where the Investigator has pre-declared antiplatelet therapy, there are no other concomitant medications required as part of the study design.

5.7. Prohibited Medications

The following drugs and devices MUST NOT be used during the treatment period unless no alternative therapy is clinically suitable.

- Anticoagulants, other than the assigned study medication, by any route with the exception of parenteral agents used as a bridge when starting or resuming study drug as per approved local label for subject's study drug;
- Fibrinolytic agents, if required to treat acute MI or pulmonary embolism (PE), require study medication interruption and consideration of a transfusion of fresh frozen plasma;
- Dual antiplatelet therapy is prohibited while on study medication except for rare occasions such as for 3 months post coronary stenting (Section 3.1, post TAVI stenting). Examples of dual antiplatelet therapy include aspirin plus a $P2Y_{12}$ antagonist such as clopidogrel. Single antiplatelet therapy with any antiplatelet agent is permitted as described throughout this protocol.
- Chronic use of NSAIDs including both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors other than aspirin for >4 days/week;
- The use of P-glycoprotein (P-gp) inhibitors during this study shall be in accordance with the approved local label for the subject's study medication except as listed below.
    - Systemic use of P-gp inhibitors such as ketoconazole, itraconazole, erythromycin, and clarithromycin may require adjustment of study medication based on the approved local label for the subject's study medication. P-gp inhibitors are generally prescribed for short-term use (≤3 weeks). When required use of P-gp inhibitors necessitates the temporary interruption of study medication, or dose reduction for the study drug Edoxaban, the subject should restart study medication after completing treatment with the P-gp inhibitor. Topical use of these medications is allowed while taking study medication.
- Other investigational drugs or devices.

The Investigator is encouraged to contact CRO medical monitor if he/she would like to discuss concomitant medications for a particular subject.

If a subject can safely stop the prohibited concomitant medication (e.g., two-week course of ketoconazole, etc.), then study medication can and should be resumed according to approved local label (usually the day after the last dose of the prohibited concomitant medication). Regardless of the duration of study medication interruption, once the prohibited concomitant medication is stopped, study medication may be resumed.

Information regarding concomitant medications will be collected with start date, stop date, drug name, dose and dosing regimen.

If required as part of standard of care, a reversal agent may be used in accordance with locally approved label.

5.8. Subject Withdrawal/Discontinuation

The intended duration of the two treatment regimens is up to 36 months. Subjects must stay on the assigned OAC-based regimen as much as possible.

Discontinuation of the assigned regimen is mandatory if the CrCL falls below 15 mL/min on two consecutive occasions or if subject is placed on dialysis. If the Investigator doubts the accuracy of the CrCL value calculated with the Cockcroft-Gault formula (Section 17.7), he/she may consider calculating CrCL using a 24-hour urine collection, for confirmatory purposes. If a subject's CrCL, calculated with either the Cockcroft-Gault formula or 24-hour urine collection, recovers to > 15 mL/min, the subject should resume study regimen in line with the applicable labels.

For subjects with a suspected transient decrease in CrCL < 15 mL/min it is recommended that repeat testing of CrCL occur after corrective action is taken or when the medical condition that caused the worsening renal function resolves. The timing of the repeat testing is at the discretion of the Investigator and will vary depending on the nature of the medical condition (e.g., 1-2 weeks for urinary tract infection or over diuresis vs. several weeks to months for glomerulonephritis).

If other clinical contraindications for any study medication develop (according to the label of the respective drug), the study medication must be discontinued (or dose decreased if applicable). If the contraindication resolves, the respective study medication is restarted. During each interruption of anticoagulant or antiplatelet therapy, subjects are evaluated to determine whether the subject can safely resume the study drug. A post-randomization change in health status that results in the subject meeting one or more of the exclusion criteria should only lead to interruption or discontinuation of the assigned medications if the change in health status implies a contraindication according to the drug labels.

Study medications are permanently discontinued if the subject refuses continuation of any medication in the assigned study regimens.

All subjects are followed through to the termination of the study irrespective of changes in the antithrombotic regimen. Clinical follow-up before the end of the study is only terminated at the explicit documented request of the subject or his/her death.

All study drug start and stop dates are captured in eCRF together with the reason for interruption or discontinuation.

5.8.1. Reasons for Study Drug Interruption/Discontinuation

Any reason for study drug interruption/discontinuation will be recorded in the eCRF. Such reasons include, but are not limited to the following:

- Reasons Related to AE:
    - Initiating or continuing study drug would place the subject at undue hazard as determined by the Investigator: in particular treatment failure or events, e.g., thrombosis, related to non-compliance with the anticoagulant regimen
    - When subjects reach a primary endpoint or a key safety endpoint, the treating physician needs to decide if OAC medication will be permanently discontinued, interrupted, modified or continued. In case of intracranial bleeding the protocol mandates stopping the study treatment.
    - SAE or other safety concern that is related to study drug treatment;
    - Concurrent increase in aspartate transaminase (AST)/alanine transaminase (ALT) > 3 X upper limit of normal (ULN) and bilirubin > 2 X ULN in the absence of a known cause (e.g., viral hepatitis, cholelithiasis) and where a causal relationship cannot be ruled out;
    - Major life-threatening bleeding (as defined in the CEC Charter, also see Section 17);
    - CrCL decreased to <15 mL/min, confirmed by repeat testing at least one week later, or need for renal dialysis.
- Death;
- Withdrawal of Informed Consent;
- Lost to Follow-up (every attempt will be made by the Investigator to avoid having subjects “lost to follow-up”);
- Pregnancy;
- Termination of all or part of the study by the Study Oversight Committee acting in concert with the DSMB and the Sponsor.
- Post randomization changes (other than CrCL decreased to <15 mL/min or need for renal dialysis) in health status related to study exclusion criteria should not automatically lead to study drug interruption or discontinuation unless continuing study drug places the subject at undue hazard as determined by the Investigator. Such situations should be handled on a case-by-case basis. The Investigator should consult with the CRO medical monitor if a subject has a post randomization change in health status that puts the subject into an exclusion criterion.

Those subjects who discontinue study participation after the initiation of study medication will have study procedures terminated at the time of discontinuation from study with the EOT Visit (Section 6.5). If the subject discontinued study treatment due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

5.8.2. Subjects with Study Drug Interruptions/Discontinuations

The Investigator should call the CRO medical monitor in case of any questions regarding how to handle a study medication interruption and/or discontinuation.

Suspension/Interruption: The date/time of the last dose, the reason for the interruption, and other required details will be recorded in the eCRF. Reasons for interruption include but are not limited to: development of clinical contraindications for any study drug (according to the label of the respective drug). During each interruption of anticoagulant or antiplatelet therapy, subjects are evaluated to determine whether the subject can safely resume the study drug.

Discontinuation: The date/time of the last dose, the reason for the discontinuation, and other required details will be recorded in the eCRF. For some potential reasons for discontinuation of study drug see Section 5.8.1 and locally approved drug label.

During a study drug interruption or after study drug discontinuation, a subject can be placed on another antithrombotic therapy per local guidelines and Investigator discretion.

All randomized subjects, including those who discontinued study medication, will be followed through the overall end of the study for the primary and secondary efficacy and safety endpoints and SAEs. If the subject has an onsite visit, it is expected that vital signs will be obtained along with any laboratory assessments deemed appropriate by the Investigator.

If a subject who discontinues study drug also withdraws consent, in writing, for participation in the study, the protocol-specified consent withdrawal procedures (Section 5.8.3) must be completed.

If the subject interrupts (or discontinues) study drug due to an AE, the Investigator will follow the event until it has resolved or stabilized.

5.8.3. Withdrawal of Consent from Study Participation

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw consent for participation in the study at any time and for any reason without prejudice to his/her future medical care by the physician or at the institution.

If a subject withdraws consent to participate in the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of consent withdrawal and including the date of the final dose of study medication. The Investigator will clearly document the reason for consent withdrawal in the medical record and will complete the associated eCRF. Under no circumstances will a subject have to undergo any study visit if he/she has expressed the will to leave the study; however, every attempt should be made to have the subject complete the 30-day Follow-up Visit (Section 6.6), be followed until the end of the study for study endpoints and SAEs (Section 6.7), and provide the subject with the information needed for transition to standard of care VKA (Section 6.5.1). If this is not possible, the subject will be offered the opportunity to consent to one of the following:

- Providing information about his/her own health status by telephone or other means until the 30 days post last dose,
- Allowing the query of their medical records,
- Allowing the use of public databases to determine subject status until the end of the study.

5.8.4. Subject Replacement

As an endpoint study with enrollment continuing until the required number of adjudicated events are reached, there is no need to formally replace a subject.

5.8.5. Subject Re-screening Procedures

There will be no re-screening of subjects for this study.

6. STUDY PROCEDURES

6.1. Screening Visit

From 12 hours to 5* days, i.e., until 23:59 of the 5th* day after the successful TAVI and prior to randomization, all screening procedures will be completed. See Table 17.1 for a listing of all screening procedures.

The following activities will be performed 12 hours and 5* days, i.e., until 23:59 of the 5th* day after the successful TAVI (See inclusion criteria #1 for definition of successful TAVI), **prior to randomization and after obtainment of written informed consent (no screening procedures may be performed unless written informed consent has been obtained):**

*If subject is waiting on a decision on pacemaker surgery, then can extend to 7 (7th) days

The informed consent form (ICF) must be signed by the subject before any study-specific procedure including randomization. A Screening eCRF must be completed for every subject with a signed ICF. Any protocol-specified study qualification procedures/tests not already done as part of routine care will need to be conducted after the ICF has been signed and before randomization.

- Enter subject into IXRS
- Check the most recent results from local laboratory tests done within the 15 days prior to randomization against the inclusion/exclusion criteria. Creatinine and complete blood count (CBC) must be available from blood draws after TAVI with the subject being clinically stable. CrCL should be calculated by the Cockcroft-Gault formula as described in Section 17.7. For subjects already on a VKA, review and record most recent INR results
- Record demographic information (date of birth/age, sex, ethnicity, and race)
- Record medical / surgical history (including bleeding history)
- Eligibility evaluation (inclusion and exclusion criteria). No subject may be randomized unless all eligibility criteria are met.
- Serum pregnancy test for female subjects who are of childbearing potential.

6.2. Randomization Visit (Day 1)

Randomization must take place within the evening of the day of TAVI and 5* days, i.e., until 23:59 of the 5th* day provided that the TAVI procedure has been judged as successful (See inclusion criteria #1 for definition of successful TAVI), and the subject is qualified based on all the protocol defined inclusion/exclusion criteria. Randomization should occur as soon as possible after signing the informed consent, given eligibility is confirmed.

*If subject is waiting on a decision on pacemaker surgery, then can extend to 7 (7th) days

- Check subject against inclusion/exclusion criteria including the most recent lab results.
- Record type of TAVI device inserted into subject in the eCRF

- Enter elements for EuroSCORE 1, EuroSCORE 2, Society of Thoracic Surgeons (STS), CHAD, and HAS-Bleed scores into the eCRF
- Contact IXRS for randomization and pre-declaration of OAP.
- Prior to any study drug administration or other tests, the subject must complete the PACT-Q1 and EuroQoL (EQ-5D-5L) questionnaires. These will be collected and uploaded into the data base by the CRO via the eCRF.
- If ECG was performed as part of routine medical practice, record the results. If not obtained as part of routine medical practice, collect a pre-dose ECG for baseline measurement and record results.
- Update medical / surgical history (including bleeding history) since screening
- Physical Examination including
    - Record vital signs (blood pressure and heart rate after the subject has been resting at least 5 minutes in a sitting position; body temperature, and weight)
    - Record height
- Record prior (since screening) medications and review as per exclusion criteria.
- If echocardiogram (transthoracic echo [TTE] or transesophageal echo [TEE]) was performed pre-TAVI per local standard of care, the information will be recorded as specified in the eCRF.
- Draw blood for analysis by an accredited/certified local laboratory (Section 9.9) (if recent [within the 15 days before randomization] are available from standard of care, these values may be used instead of requiring an additional blood draw). Creatinine and CBC must be available from blood draws after TAVI and the subject must be clinically stable. CrCL should be calculated by the Cockcroft-Gault formula as described in Section 17.7 and the results need to be available prior to the 1st dose of study drugs for subjects randomized to Edoxaban. Include a liver panel only if recent (within the 15 days before randomization) results are not already available.
- For childbearing potential female subjects, a urine pregnancy test (e.g., dipstick test) will be performed at Randomization, 3 months, 12 months, 24 months, and End of Treatment Visits. Furthermore, pregnancy tests will be carried out whenever there are clinical indications for the existence of a pregnancy.
- First administration of assigned study medication **within 24 hours of randomization;** however, NO EARLIER than the morning after successful TAVI.
- Record date/time of first study medication administration in eCRF
- Instruct subject on the use of study medication (see Section 3.1)
- Instruct subject on the use of the memory aid
- Dispense assigned OAC

  - Daiichi Sankyo supplies study subjects with Edoxaban. VKA and OAP may be supplied by the site or via prescriptions issued either by the site or attending physician. See Section 3.1 about OAP administration.
- Assessment and recording of (S)AEs and suspected clinical events will start immediately after signed informed consent and continue until 30 days after the end of treatment with study medication.

The randomized treatment strategy is implemented after randomization without any undue delay.

6.3. Prior to Discharge or Transfer to Another Hospital or Hospital Department

No study-related actions, unless driven by a sudden medical need, are required before a subject will be either discharged or transferred to another hospital department or hospital such as a rehabilitation clinic; however, discharge date needs to be captured in the eCRF.

6.4. Continued Treatment Visits

For all subjects randomized to VKA, all INR measurement shall be performed by local accredited/certified labs at a frequency determined by the subject's treating physician (monthly preferred). Trained and certified subjects may perform INR testing themselves using an approved point-of-care device but need to provide the results to the Investigator and the results need to be recorded in the eCRF.

  - Dose adjustments in VKA will be made to achieve and maintain an INR of 2.0 to 3.0 (numbers inclusive) [Japan: 1.6 to 2.6 in subjects aged ≥70 (numbers inclusive)] throughout the study.

For all subjects, study visits (either as on-site or at the subject's current place of living, must be conducted by the Investigator or their appropriately trained designee) at 3 months (± 14 days), 6 months (± 14 days), and at 6 month intervals (± 14 days) thereafter through the end of the study which may be 36 months or longer (i.e., event driven study).

The following procedures will be performed during study visits:

- Check and record any changes in concomitant medication
- Assessment and recording of (S)AEs and suspected clinical events since last visit
- Assessment of any hospitalization for cardiovascular causes (such as shock, arrhythmia, cardiac rupture, stroke, aneurysms, stent occlusions, etc.) or bleeding
- Record vital signs (blood pressure and heart rate after the subject has been resting at least 5 minutes in a sitting position; body temperature and weight)
- Only if medically necessary, 12-lead ECG and recording of the results
- For childbearing potential female subjects, a urine pregnancy test (e.g., dipstick test) will be performed at 3 months, 12 months, 24 months, and End of Treatment

Visits. Furthermore, pregnancy tests will be carried out whenever there are clinical indications for the existence of a pregnancy.

- Blood draw for analysis by an accredited/certified local laboratory for all subjects (see Section 9.9) or if results are available from standard of care and are within 15 days prior to the visit these values may be used instead of requiring an additional blood draw.
    - *The liver function panel needs to be run at the 6 Month and 12 Month Visits and if clinically necessary at other times*.
    - In subjects randomized to VKA, obtain the subject's INR records from previous visit(s) through to the current visit and adjust dose as necessary to obtain/maintain an INR of 2.0 to 3.0 (numbers inclusive) [Japan: 1.6 to 2.6 in subjects age ≥70 (numbers inclusive)]. INR measure is only mandated if the previous measurement was performed more than 3 months prior to this visit or the target INR has been shown difficult to achieve.
- Record all INR results for subjects on VKA since subject's last visit in eCRF (if not recorded earlier in the eCRF).
- Review and record study regimen compliance and drug interruptions
    - Collect any unused study medication
- Dispense Edoxaban and inform subjects that VKA and OAP will be provided or prescribed from the study site or treating physician, as needed. If approved by the local regulatory authority, site should re-dispense the VKA Patient Prescription Aid at each study visit. Review dosing records for all subjects, and VKA and APT therapy regime and prescription information. All dosing information should be recorded in source on the applicable logs, in EDC, and for Edoxaban only, also in IXRS.
- If echocardiogram (TTE or TEE) has been done at any time as medically indicated or as per local standard of care in the individual centers, the results will be recorded as specified in the eCRF.

At Months 3 and <u>either</u> Month 12 or at EOT (whichever comes first):

- Have the subject complete the PACT-Q2 and EQ-5D-5L questionnaire which will be provided separately to the sites. This should be done before other procedures are conducted.

6.5. End of Treatment (EOT) Visit

As an event driven study, the subjects will continue on treatment until the study is stopped (the end of the study) due to 320 adjudicated events (from approximately 2500 subject years) will have been reached, or they permanently discontinue from the study (for any reason). Subjects enrolled late in the study may be terminated from the study after a minimum of 6 months on treatment. The end-of-treatment (EOT) visit is the subject's last treatment visit independent of whether this is the end of the study or occurs at time of their withdrawal or discontinuation for any reason. Subjects will <u>also</u> have a Post-treatment Follow-up Visit 30 days (± 7 days) after the EOT Visit.

The following procedures will be performed:

- *If EOT is prior to 12 months, have the subject complete the PACT-Q2 questionnaire and EQ-5D-5L questionnaire; if after 12 months on treatment, this is not done as it was captured at 12 months*.
- Check and record any changes in concomitant medication
- Review and record study regimen compliance and drug interruptions
- Assessment and recording of (S)AEs and suspected clinical events since last visit
- Assessment of any hospitalization for cardiovascular causes (such as shock, arrhythmia, cardiac rupture, stroke, aneurysms, stent occlusions, etc.) or bleeding
- Record date/time of final dose of study medication
- Collect all unused study drug(s)
- For childbearing potential female subjects, a urine pregnancy test (e.g., dipstick test) will be performed.
- Draw blood for analysis by an accredited/certified local laboratory for all subjects see Section 9.9 or if results are available from standard of care and are within 15 days prior to the visit these values may be used instead of requiring an additional blood draw;
    - In subjects randomized to VKA, obtain the subject's INR records from previous visit(s) through to the current visit (inclusive)
- Physical examination (details under Section 6.2)
- Record vital signs (blood pressure and heart rate after the subject has been resting at least 5 minutes in a sitting position; body temperature, and weight)
- If not part of standard of care, a 12-lead ECG will be performed. The results of any ECG will be recorded in the eCRF
- If echocardiography (TTE or TEE) has been performed at any time as medically indicated or as per local standard of care for TAVI, the results will be recorded as specified on eCRF.
- Confirm consent to participate in Post Discontinuation/Follow-up Contact;

Transition subject to appropriate medication (Section 5.2.1)**Note: In subjects with early permanent discontinuation of the assigned therapy every attempt made to have the Follow-up Visit performed.**

6.5.1. Transition from Study Medication to Standard of Care VKA

Before transitioning to open-label VKA, all non-transition kit study supplies must be retrieved from the subject to avoid drug administration errors. For information on transitioning of medication, see Section 5.2.1.

The subjects on Edoxaban will use the Sponsor provided transition kit to transition from Edoxaban to a VKA. The choice of VKA will be made by the Investigator in consultation with the subject's personal physician and per local guidelines. More information on this transition from Edoxaban to open-label VKA is available in

Section 5.2.1. Subjects on VKA may be transitioned to another locally approved VKA following local guidelines.

6.6. Post-treatment Follow-up Visit

The Follow-up Visit will be 30 days (± 7 days) after the last study treatment.

The Follow-up Visit activities are listed below:

- Perform physical examination;
- Record vital signs (blood pressure and heart rate after the subject has been resting at least 5 minutes in a sitting position; body temperature, and weight);
- Check INR and recommend any dose adjustments to subject's personal physician;
- Blood draw for analysis by an accredited/certified local laboratory, the clinical laboratory tests (see Section 9.9) or if results are available from standard of care and are within 15 days prior to the visit these values may be used instead of requiring an additional blood draw;
- Assessment and recording of (S)AEs and suspected clinical events since last visit; Assessment of any hospitalization for cardiovascular causes (such as shock, arrhythmia, cardiac rupture, stroke, aneurysms, stent occlusions, etc.) or bleeding;
- Record any changes in concomitant medications;
- Confirm consent to participate in Post Discontinuation/Follow-up Contact;
- For childbearing potential female subjects, a urine pregnancy test (e.g., dipstick test) will be performed.

6.7. Post Discontinuation/Follow-up Contact

- Subjects (unless they refuse to participate) will be called approximately every 6 months (± 1 month) until the Sponsor determines the end of the study to assess the subject's vital status, occurrence of potential endpoint events, or any SAEs. This information may be obtained from relatives, public records, or the treating physician. Should the subject choose to not receive phone calls, the site may attempt to retrieve this information from viewing the subject's medical records or public records.

7. OUTCOME ASSESSMENTS

7.1. Bleeding

Bleeding for the purpose of endpoints will be classified according to the ISTH definitions (see Section 17.1.1 and Section 9.1.1). Bleeding events will also be classified according to BARC (Section 17.1.3), TIMI (Section 17.1.2), and GUSTO (Section 17.1.4) classifications.

7.2. Primary Efficacy Parameters

NACE, i.e., the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (ISTH definition)

7.3. Primary Safety Parameters

Major bleeding (ISTH definition)

7.4. Secondary Endpoints (All Exploratory)

7.4.1. Secondary Efficacy Endpoints

- NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (TIMI definition);
- NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (BARC 3 or 5 definition);
- NACE defined as the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major and moderate bleeding (GUSTO definition);
- Major Adverse Cardiac Events (MACE), defined as the composite of all-cause death (excluding adjudicated non-cardiac death), MI, or repeat coronary revascularization of the target lesion;
- Major Adverse Cardiac and Cerebrovascular Events (MACCE), defined as the composite of all-cause death (excluding adjudicated non-cardiac death), MI, stroke (ischemic, hemorrhagic, or undetermined), or repeat coronary revascularization of the target lesion;
- Cardiovascular mortality
- Stroke (ischemic, hemorrhagic, or undetermined);
- Stroke (ischemic);
- Stroke (hemorrhagic);
- Stroke (undetermined)
- Fatal stroke (ischemic, hemorrhagic, or undetermined);
- Non-fatal stroke (ischemic, hemorrhagic, or undetermined);
- SEE;
- Myocardial Infarction;
- Valve thrombosis;

7.4.2. Secondary Safety Endpoints

- Bleeding defined as TIMI major or minor, BARC 3 or 5, and GUSTO moderate or severe;
- Bleeding defined as ISTH major and CRNM; TIMI major/minor bleeds or requiring medical attention; BARC 2, 3 or 5; and GUSTO moderate or severe;
- Bleeding defined as ISTH CRNM, TIMI minor or requiring medical attention, BARC 2, and GUSTO moderate;
- All bleeding that are not ISTH major, CRNM, TIMI minimal, BARC 1 non-actionable, and GUSTO mild;
- Any bleeding;
- Intracranial hemorrhage;
- Life-threatening bleeding;
- Fatal bleeding (fulfilling the ISTH major bleeding definition);
- Non-fatal major bleeding (ISTH definition);
- All-cause mortality;
- Cardiovascular mortality;
- Safety parameters such as (serious) adverse events, laboratory parameters, ECG and vital signs

7.4.3. Other Endpoints

- Number of hospital admissions, defined as ≥ 24 h stay in the hospital, due to cardiovascular causes (post TAVI and non-TAVI procedure related), including but not limited to overall, for bleeding, SEE, venous thrombosis, shock, arrhythmia, cardiac rupture, stroke, aneurysms, stent occlusions, etc.
    - Note: Hospital admissions due to cardiovascular causes include, but are not limited to the Emergency Department, ICU, and cardiovascular ward.
- Treatment satisfaction as assessed by the PACT-Q
- Health related quality of life as assessed by the EQ-5D-5L Questionnaire
- Optional: Sub-studies not interfering with the main study may be added including such as the assessment of biomarkers of hemostasis/coagulation and of cardiovascular risk such as but not limited to WBCT, TEG, and MEA, Hs-TnT, GDF-15, and cystatin-C.

All clinical endpoints will be analyzed as time to first occurrence of any of its components.

All relevant NACE components will be adjudicated by the CEC in a blinded manner. For all clinical endpoints blindly adjudicated by the CEC, the CEC's interpretation prevails and will be used in the statistical analysis.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

Not applicable

8.1. Immunogenicity

Not applicable

8.2. Pharmacogenomic Analyses

Not applicable

9. SAFETY EVALUATION AND REPORTING

Safety assessments that are components of the study endpoint assessments (e.g., bleeding endpoints) are detailed in Section 7.3 and Section 7.4.2 and must be collected in the AE/Outcome eCRF page(s).

9.1. Adverse Event Collection and Reporting

All clinical AEs (see Section 9.3.1 for definitions) occurring after the subject signs the Informed Consent Form and up to 30 days after the last dose of study medication (i.e., the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event eCRF page.

Subjects who permanently discontinue study medication but continue in the study will be followed up every 6 months for collection of vital status (not vital signs) including collection of SAE and/or endpoint event reporting until the end of study (see Section 6.7).

Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to Informed Consent will be recorded as part of medical history.

All serious adverse events (SAEs), are to be reported according to the procedures in Section 9.6.

- All laboratory results, vital signs, ECG, and any other imaging results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (i.e., not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.
- At each visit, the Investigator or qualified designee will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject, or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.3. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

For events that are defined as serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring

hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE.

Pre-planned (prior to signing the ICF) procedure or treatment requiring hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 9.3.4 for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

Investigator should follow subjects with adverse events until the event has resolved or the condition has stabilized. In case of unresolved adverse events including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they become clinically not relevant.

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

Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).

Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g., allergic pollinosis).

Conditions that started or deteriorated after the first dose of drug will be documented as adverse events; these include intercurrent illnesses.

9.1.1. Bleeding

All bleeding events will be reported in the eCRF as either an AE or SAE depending upon the seriousness criteria (see Section 9.6 for additional details).

Bleeding requiring medical attention will be adjudicated by the CEC based on ISTH (see Section 17.1.1). Bleeding events that do not require medical attention will be classified as minor bleeding without CEC adjudication.

The CEC will require all available details about the bleeding event and related information to allow successful objective adjudication of the event. Details may include, but are not limited to, information such as the following:

- Location of the bleeding
- Timing of the bleeding event: association with adherence of study drug, medications, and procedures

- Treatment for bleeding event, including notes or summary of the recommendations from a healthcare professional from whom medical treatment was obtained
- Magnitude of the bleeding (including size if skin or subcutaneous hematoma)
- Hemoglobin levels at randomization and at the time of the bleeding event, lowest value, pre- and post-transfusion values, and after resolution of the bleeding event
- Diagnostic tests for the evaluation of the bleeding such as endoscopy (gastrointestinal bleed), ear, nose, and throat consult (ear, nose, throat bleed), urology consult (hematuria or urogenital bleeding), surgical consult (skin and soft tissue, including intraabdominal bleeding), gynecological consult (uterine or vaginal bleeding), neurological consult (intracranial bleed), or ophthalmology consult (intraocular bleed)
- Diagnostic scans (CT scans or MRIs), ultrasounds, or x-rays performed to evaluate the bleeding (intracranial bleed)
- Any other information that can be of help to the CEC to allow successful objective adjudication of the bleeding event.

9.2. Events of Special Interest

9.2.1. Combined Elevations of Aminotransferases and Bilirubin

There is no clinically concerning signal of drug-induced liver injury associated with Edoxaban based on the extensive global Phase 3 experience involving over 34 048 Edoxaban subject-years exposure (with median drug exposure of ≈2.5 years among 18 010 Edoxaban treated subjects).

However, there will be ongoing monitoring of hepatic events with particular attention to combined elevations of aminotransferases and bilirubin (ALT or AST > 3 x ULN with simultaneous total bilirubin levels > 2 x ULN), without evidence of cholestasis (ALP > 2 x ULN is considered evidence of possible cholestasis) where no etiology for hepatocellular damage has been identified and a causal relationship to study drug cannot be ruled out.

Combined elevations of aminotransferases and bilirubin meeting the laboratory criteria of a potential Hy's Law case [ALT or AST ≥ 3 x ULN with simultaneous total bilirubin levels ≥ 2 x ULN] irrespective of whether they are serious or non-serious and whether causally related or not to study drug should always be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event following the procedures outlined in Section 9.5.

In cases of liver laboratory abnormalities, or where there is evidence of liver dysfunction, it is important to ensure that the nature and the extent of liver injury is identified, and study subjects are monitored until the liver laboratory assessments return to normal.

If the subject discontinues study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations which depending upon the clinical situation MAY include:

- Abdominal ultrasound;
- Hepatitis A, B, C, and E screening (anti-HAV IgM, HBsAg, anti-HCV plus viral titer, and evaluation for Hep E);
- Antinuclear antibody (ANA) and anti-SmAb;
- Cytomegalovirus (CMV);
- Epstein Barr virus (EBV);
- Additional evaluations as deemed appropriate by the Investigator to exclude other causes of liver enzyme and bilirubin elevations.

Subject's follow-up will be required until the values (transaminases, total bilirubin, and direct bilirubin) return to baseline. All clinically significant hepatic enzyme abnormalities and/or hepatic events must be documented in the eCRF. An adjudication dossier should be submitted for events that led to study drug discontinuation or were reported SAEs, where no alternative etiology has been found after work-up and where causal relationship to study drug cannot be ruled out.

The subject may re-start study medication if considered appropriate by the Investigator.

9.2.2. Reporting of Pregnancy/ Exposure in Utero

The Sponsor or designee must be notified of any subject that becomes pregnant while participating in a clinical study. All pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a subject, which occurs during the study.

Notification of the pregnancy should be submitted in the eCRF (AEs of special interest) within 24 hours and reported using Exposure in Utero Reporting form (paper form) and reported to the CRO medical monitor who will contact the Sponsor.

If the pregnancy is to be terminated, the anticipated date of termination should be provided. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting an SAE. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy in a follow-up Exposure in Utero Reporting Form.

9.3. Adverse Event

9.3.1. Definition of Adverse Event

Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can

therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered adverse events.

9.3.2. Unexpected Adverse Event

An unexpected AE is an AE, the nature or severity of which is not consistent with the reference safety information of any of the study medications or co-administered medications. The designation of expected or unexpected must be decided from the perspective of previously described AEs, not on the basis of what might be anticipated from pharmacological properties of a medicinal product. Determination of expectedness is the responsibility of Daiichi Sankyo and not the Investigator.

9.3.3. Expected Adverse Event

An expected AE is an event which is described in the reference safety information of the study drugs in nature, severity or incidence.

9.3.4. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term “life-threatening” in the definition of “serious” 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 (International Council on Harmonisation [ICH] E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasia or development of drug dependency or drug abuse.

Notes:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the Informed Consent Form) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.3.5. Severity Assessment

The following definitions should be used to assess intensity of adverse events:

- Mild: Awareness of sign or symptom, but easily tolerated, i.e., does not interfere with subject's usual function.
- Moderate: Discomfort enough to cause interference with usual activity.
- Severe: Incapacitating with inability to work or do usual activity, i.e., interferes significantly with subject's usual function.

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event whereas the event itself; however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on subject/event outcome at the time of the event.

9.3.6. Causality Assessment

The Investigator should assess causal relationship between an adverse event and the study drug on the basis of his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- 1 = Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

    or
  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- 2 = Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

9.3.7. Action Taken Regarding Study Drug(s)

- 1 = Dose Not Changed: No change in study drug dosage was made.

- 2 = Drug Withdrawn: The study drug was permanently stopped.
- 3 = Dose Reduced: The dosage of study drug was reduced.
- 4 = Drug Interrupted: The study drug was stopped for a period of time.
- 5 = Dose Increased: The dosage of study drug was increased.
- Not Applicable: (e.g., Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment)

9.3.8. Other Action Taken for Event

1 = None: No treatment was required.

2 = Concomitant medication required: Prescription and/or over-the-counter medication were required to treat the adverse event.

3 = Concomitant medication permanently discontinued: Prescription and/or over-the-counter medication other than the assigned anticoagulant-based regimen was permanently discontinued due to the adverse event.

4 = Concomitant medication temporarily interrupted: Prescription and/or over-the-counter medication other than the assigned anticoagulant-based regimen was temporarily interrupted due to the adverse event.

5 = Other.

9.3.9. Adverse Event Outcome

1 = Recovered/Resolved: The subject fully recovered from the adverse event with no residual effect observed.

2 = Recovered/Resolved with Sequelae: The residual effects of the adverse event are still present and observable. Include sequelae/residual effects.

3 = Not Recovered/Not Resolved: The adverse event itself is still present and observable.

4 = Fatal

5 = Unknown

The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved adverse events including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they become clinically not relevant.

9.4. Timing of Adverse Event Reporting

All AEs must be recorded and reported from the stated starting point of the clinical trial (immediately after signing ICF) including AEs taking place during the administration of other drugs. Even if the subject has not yet received the investigational treatment, untoward medical occurrences have to be treated as AEs.

The period of AE reporting is defined as follows:

AEs that occur within 30 days after the last dose of the assigned study treatment, which are reported to the Investigator (regardless of the date of a Follow-up Visit) must be recorded in the eCRF.

9.5. Reporting SAEs/AEs

9.5.1. Documentation

To effectively evaluate the safety profile of the study treatments, this study will report all (S)AEs occurring after the subject signs the IC and as long as the subject remains in the study or until the study is terminated by the Sponsor (i.e., the end of the study), whether observed by the Investigator or reported by the subject. All AEs will be recorded on the AE/Outcome eCRF page(s) and include:

- Any components of the study endpoint assessments (see Section 7);
- AEs that meet seriousness criteria (see Section 9.3.4);
- AEs that result in interruption or discontinuation of the assigned study treatment;
- Any other AE.

All laboratory results and vital signs should be evaluated by the Investigator regarding clinical significance. Isolated abnormal laboratory results or vital sign findings that are not part of a diagnosis should be reported as AEs or SAEs. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to IC will be recorded as part of medical history.

All SAEs are to be reported as long as the subject remains in the study or until the study is terminated by the Sponsor (i.e., the end of the study) and according to the procedures in Section 9.6. Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization).

AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.3.5 and Section 9.3.6. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

9.6. Serious Adverse Event Reporting–Procedure for Investigators

- SAEs (see Section 9.3.4 for definition)
- Serious events that are also efficacy endpoints (stroke, transient ischemic attack, SEE, and myocardial infarction) and/or safety endpoints (bleeding) will be exempted from SAE processing and expedited reporting but will be captured in

the eCRF. These events are exempted as they are clinically anticipated events in the target treatment population and will be periodically reviewed by the DSMB in an unblinded manner to ensure prompt identification of any clinically concerning safety issues.

- **All SAEs resulting in death regardless of whether they are waived endpoints for processing and expedited reporting will be processed by the CRO for entry into the Sponsor's global safety database**.

In case of an occurrence of an SAE, the Investigator applies the following rules:

- Ensure appropriate medical treatment and decide whether to discontinue or interrupt any of the study medications or co-administered medications.
- Complete the initial AE/Outcome eCRF page upon event awareness.
- Record the event, its management, and outcome in the eCRF page.
- For SAEs, report in the eCRF **within 24 hours** of receiving knowledge of the occurrence. In the event that all the required information is not available, the information which is available is to be sent without delay (within 24 hours), and the outstanding data relayed as soon as available thereafter. Answer any queries related to the reported SAE as soon as possible.
- For AEs of special interest, report **within 24 hours** of receiving knowledge of the occurrence as defined for SAEs above.
- For AEs, obtain all data required incl. any information which, is only available after considerable delay (i.e., hospital reports, outcomes, resolution end dates), **as soon as available**.
- Components of the study endpoint assessments which result in death must be reported as SAEs **within 24 hours** of the Investigator’s awareness.

9.7. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committee

Daiichi Sankyo and/or CRO will inform Investigators, Institutional Review Boards (IRBs)/Ethics Committees (EtCs), and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in other study centers or other studies of the investigational drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements. Detailed SAE processing, distribution and reporting will be laid out in sponsors SAE Flow Plan.

In the US, upon receipt of the Sponsor’s notification of SUSARs that occurred with the study drug, unless delegated to the Sponsor, it is the Investigator’s responsibility to inform the IRB/EtC per Sponsor’s instruction.

In the European Economic Area (EEA) states, it is the Sponsor’s responsibility to report SUSARs to all ECs.

9.8. Exposure In Utero During Clinical Studies

While this should not be applicable, should it occur, see Section 9.2.2 for further details.

9.9. Clinical Laboratory Evaluations

Information will be entered in the case report form on whether or not measured, date of measurement, and measurement results and the local laboratory ranges for the following items.

The results will be reviewed and compared to the local accredited/certified laboratory's normal ranges. The visits at which these samples will be collected are shown in the schedule of assessments (Table 17.1).

The following safety laboratory evaluations are performed:

- **Serum Chemistry Panel**
  - Creatinine
  - Sodium (Na^+)
  - Potassium (K^+)
  - Chlorine (Cl^-)
  - Blood urea nitrogen (BUN)
  - Glucose
- **Complete Blood Count (CBC) Panel:** Including Hemoglobin, Hematocrit, WBC, Platelet Count
- **INR** (only for subjects on VKA)
- **Urine pregnancy test** (e.g., dipstick test), for childbearing potential female subjects at Randomization, 3 months, 12 months, 24 months, and End of Treatment Visits.
- **Serum pregnancy test** at time of Screening for women of child bearing potential who are female subjects who are of child bearing potential.

A liver function panel (total bilirubin [conjugated/unconjugated performed when total serum bilirubin ≥ 2 mg/dL], ALT, AST, ALP) will be performed at Screening (only if a recent, within the 15 days before randomization, is not available), and at the 6 Month and 12 Month Visits.

All other assessments are collected from local laboratory results for tests done as part of routine care. Local laboratory assessments are used for parameters required to verify eligibility and for parameters that require monitoring according to local routine.

9.10. Vital Signs

Blood pressure and heart rate will be measured at all specified visits (Table 17.1) after the subject has been resting at least 5 minutes in a sitting position, along with height (only at randomization), body temperature, and body weight.

9.11. Electrocardiograms

The ECG will be recorded after the subject has rested in a recumbent position for 5 minutes or more. The date performed, results, and any clinically significant findings for will be recorded in the case report form.

If the ECG is not performed for any reason, the date and reason will be recorded in the case report form.

9.12. Physical Examinations

The Investigator or a licensed study team member will perform targeted physical examinations according to Table 17.1. As stated earlier, height is only needed once, usually at Screening.

A physical examination will consist of assessment of each of the relevant (cardiac, pulmonary, gastrointestinal, dermatologic) major body systems. If a system is not assessed, the Investigator or designee will note the reason in the source documents. Assessment of other systems, including neurological, is not required per protocol, unless determined as necessary per investigator discretion for further evaluation of a suspected AE (eg., Stroke or TIA), or suspected outcome event.

10. OTHER ASSESSMENTS

10.1. Healthcare Resource Utilization

Data for each hospitalization post TAVI but non-TAVI procedure related that are due to cardiovascular causes (such as shock, arrhythmia, cardiac rupture, stroke, aneurysms, stent occlusions, etc.), including data on admission and discharge dates, hospital ward (e.g., emergency department, intensive care unit, cardiovascular ward), admission diagnosis and status post TAVI will be collected.

- Bleeding
- Ischemic stroke
- SEE
- Myocardial infarction
- Valve thrombosis
- Other cardiovascular causes

10.2. Perception Anticoagulant Treatment Questionnaire (PACT-Q)

The Perception of Anticoagulant Treatment Questionnaire (PACT-Q) was developed to assess subjects' expectations of, and satisfaction with their anticoagulant treatment. The psychometric properties of the PACT-Q have been reported previously. The PACT-Q consists of two modules. The first module, PACT-Q1, contains 7 items, each individually scored from 1 to 5, with higher score indicating higher subjects' expectation for their treatment. The second module, PACT-Q2, is constituted of two dimensions: Convenience (11 items) and Anticoagulation Treatment Satisfaction (7 items). Items in the Convenience dimension are reversed scored, summed and rescaled on a 0 to 100 scale such that the higher the score indicates a treatment to be more convenient and less burdensome as perceived by the subject. Items in the Anticoagulation Treatment Satisfaction dimension are summed and rescaled on a 0 to 100 scale. Higher score indicates higher satisfaction with anticoagulation treatment.

The PACT-Q1 will be administered to study subjects at randomization. The PACT-Q2 will be administered to study subjects at 3 months and either12 months or the EOT whichever comes first. A copy of the PACT-Q1 and PACT-Q2 will be provided to the sites.

10.3. EuroQoL (EQ-5D-5L) Questionnaire

The EQ-5D-5L is standardized measure of health status developed by the EuroQoL Group in order to provide a simple descriptive profile and a single health status index. The EQ-5D-5L consists of two measures: 1) the EQ-5D-5L descriptive system and 2) the EQ Visual Analogue Scale (EQ VAS). The EQ-5D-5L descriptive system asks the subject to provide rating on each of the five dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS records the subject's overall health on a 0 to 100 analogue scale anchored from "best imaginable health state" to "worst imaginable health state".

The EQ-5D-5L is designed for self-completion by study subjects and takes only 1 to 2 minutes to complete. The EQ-5D-5L will be administered for study subjects at randomization, 3 months and either12 months or the EOT whichever comes first. A copy of the EQ-5D-5L will be provided to the sites.

11. STATISTICAL METHODS

11.1. Analysis Sets

In the following subsections only the analysis sets for the statistical analyses of efficacy and safety parameters are defined. Other analysis sets (e.g., health economics outcome research [HEOR]) will be defined in the Statistical Analysis Plan (SAP) as needed.

11.1.1. Intention-to-treat Analysis Set

The *Intention-to-treat Analysis Set (ITT)* consists of all randomized subjects irrespective of whether they received a single dose of study Edoxaban or VKA or not.

Analyses will be based on the randomized treatment regimen even if a subject inadvertently receives the incorrect drug(s) or dosage or has his/her Edoxaban dose adjusted (decreased/ increased) one or more times during the study. The reference date for consideration of endpoints is the date and time of randomization.

11.1.2. Modified Intention-to-treat Analysis Set

The *modified Intention-to-Treat (mITT) Analysis Set* consists of all randomized subjects who received at least one dose of study Edoxaban or study VKA according to IXRS assignment.

Analyses will be based on the randomized treatment regimen even if a subject inadvertently receives the incorrect drug(s) or dosage or has his/her Edoxaban dose adjusted (decreased/ increased) one or more times during the study. The reference date for consideration of endpoints is the date and time of first intake of study Edoxaban or study VKA.

11.1.3. Per Protocol Analysis Set

The *Per Protocol Analysis Set (PP)* consists of all randomized subjects who received at least one dose of the study regimen according to IXRS assignment and do not have any of the following major protocol violations:

- A major violation of the inclusion criteria
- An unequivocal violation of the exclusion criteria

The list of major violations will be finalized before database lock. The list and the exclusions will be confirmed in a blinded way, i.e., without knowledge of the randomized study regimen and of the clinical outcomes.

Analyses will be based on the randomized treatment regimen, even if a subject inadvertently receives the incorrect drug(s) or dosage or has his/her Edoxaban dosage adjusted (decreased/ increased) one or more times during the study. The reference date for consideration of endpoints is the date and time of first intake of study Edoxaban or study VKA.

11.1.4. Safety Analysis Set

The *Safety Analysis Set (SAF)* consists of all randomized subjects who received at least one dose of the study Edoxaban or study VKA according to IXRS assignment.

Analyses will be based on the randomized treatment regimen, even if the subject's Edoxaban dosage is adjusted after randomization, unless a subject inadvertently receives the incorrect drug(s) or dosage during the entire study, in which case the subject will be grouped according to the treatment actually received.

Note: This SAF analysis set will be used for the safety parameters (e.g., adverse events, vital signs, laboratory parameters, etc.) as described under Section 9.

11.2. General Statistical Considerations

All analyses will be performed on observed data only. No missing data will be imputed. Data on subjects who do not reach a specific endpoint will be censored in the corresponding statistical analyses.

Raw data will be presented with the exact precision (decimal points) with which it was collected.

The p-values will be presented in the end-of-text tables exactly as they are in supporting statistical documents (4 decimal points). The text and in-text tables will display p-values with three decimal places, as long as the decision for statistical significance will not be changed by rounding.

The number of decimal places to display for calculated data will be determined by the scale of measurement. No decimal places will be displayed if the smallest calculated value is ≥ 100; one (1) decimal place will be displayed when all calculated values are within the interval (10, 100), with 10 being inclusive; two (2) decimal places will be displayed when all calculated values are within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement. Percentages will be reported with exactly one decimal place.

For continuous variables, statistical summaries will include n (number of subjects with non-missing data), mean, median, standard deviation, minimum, and maximum. Means and medians will be displayed to one more decimal places than the raw or calculated data; standard deviation and other dispersion statistics will have two more decimal places; and minimum and maximum values will be displayed to the same number of decimal places as the raw or calculated data.

For categorical variables, statistical summaries will include counts and percentages. Percentages will be reported with exactly one decimal place. In general, percentages are based on the total number of subjects with information available (i.e., non-missing data). For AE and incidence-based analyses, percentages will be based on the total number of subjects in the analysis set of interest and in that treatment regimen.

Definition of terms:

'Overall Study Period': This period is defined as the time from the reference date up to an estimated Month 36/EOT (Visit 8).

'Overall Study Period + 30 days': This period is defined as the time from the reference data up to an estimated Month 36/EOT (Visit 8) + 30 days, i.e., to Month 37 (post-treatment FU visit).

'Initial dose to Final Dose + 30 days': This period is defined as the time-period between the date and time of initial dose of study Edoxaban or study VKA and the date and time of final dose of study Edoxaban or study VKA + 30 days, including study regimen interruptions.

Follow-up is censored at the last date of known follow-up status in subjects with incomplete follow-up. Investigators are instructed to complete follow-up as much as possible irrespective of changes or discontinuation of study medication.

When using the ITT analysis set, the reference date is the date and time of randomization, whereas in mITT and PP analyses, the reference date is the date and time of first intake of study Edoxaban or study VKA.

The main analyses of adjudicated primary and secondary exploratory endpoints (Section 7.2, Section 7.3, and Section 7.4, respectively) will be based on ITT analysis set and takes the first adjudicated event during the 'overall study period' into account.

However, in supplemental analyses, other combinations of analysis sets and analysis periods may be considered to evaluate the robustness of the main analyses on adjudicated safety or efficacy endpoints. Details on these analyses will be described in the SAP.

11.3. Study Population Data

Subject disposition will be summarized for each randomized treatment regimen and in total for the ITT analysis set. The number of subjects for each defined analysis set by treatment regimen will also be tabulated.

The demographic and baseline characteristics including baseline disease status will be summarized descriptively by treatment regimen for the ITT, mITT, PP, and SAF analysis sets.

Exposure to study drugs (Edoxaban, VKA, $P2Y_{12}$ antagonist, and ASA) will be summarized using descriptive statistics by treatment regimen for the mITT, PP and SAF analysis sets. Interruptions and permanent discontinuations (see Section 5.8) will be summarized by treatment group for the same analysis sets.

The time in therapeutic range (TTR) (INR: 2.0 to 3.0, numbers inclusive) [Japan: 1.6 to 2.6 in subjects age ≥70 (numbers inclusive)] will be estimated for each subject randomized to the VKA-based antithrombotic regimen using the interpolation method of Rosendaal.[26]

11.4. Statistical Analyses

For each of the primary and secondary efficacy and safety endpoints, appropriate summary statistics (e.g., event rate) including 95% confidence interval (CI) will be provided.

For each of the endpoints, the time from reference date to the first occurrence of an event (based on CEC adjudication), is analyzed using a Cox proportional hazard model with treatment regimen as a factor and all the stratification factors from the randomization (IXRS) as covariates, dose adjustment [yes, no], to provide point estimates and 95% CI for the hazard ratio (HR). Depending on the analysis period used in the statistical analysis, subjects without an occurrence of an event will be censored at the last date of the analysis period or at the last date of known outcomes status. The latter is determined on an individual basis for subjects with incomplete follow-up.

The parameter estimate β (= ln (Hazard ratio), its standard error, p-value, and 95% confidence limits are calculated according to the maximum partial likelihood method, with Breslow's approximation for ties (SAS PHREG procedure).

For time to first event analyses, cumulative event rates over time are summarized using the Kaplan-Meier method as appropriate.

11.4.1. Analysis of the primary endpoint(s)

The primary efficacy endpoint is *NACE*, i.e., the composite of all-cause death, MI, ischemic stroke, SEE, valve thrombosis, and major bleeding (ISTH definition).

The primary safety endpoint is *major bleeding (ISTH definition)*.

There are 4 primary hypotheses that will be tested in hierarchical order:

- Hypothesis (1):
  - The Edoxaban-based regimen is noninferior to the VKA-based regimen with regards to NACE.
- Hypothesis (2):
  - The Edoxaban-based regimen is noninferior to the VKA-based regimen with regards to major bleeding (ISTH definition).
- Hypothesis (3):
  - The Edoxaban-based regimen is superior to the VKA-based regimen with regards to major bleeding (ISTH definition).
- Hypothesis (4):
  - The Edoxaban-based regimen is superior to the VKA-based regimen with regards to NACE.

The analysis set and analysis periods to be used for the main analysis related to these four hypotheses are presented below:

Table 11.1: Statistical Analysis Hierarchy for Primary Parameters

Hypothesis	Endpoint	Primary Analysis Set	Primary Analysis Period
(1)	NACE	ITT	Overall study period
(2)	Major bleeding (ISTH def)	ITT	Overall study period
(3)	Major bleeding (ISTH def)	ITT	Overall study period
(4)	NACE	ITT	Overall study period

To control the type-I error rate, these four hypotheses will be tested in a hierarchical manner:

- Step (1): The Edoxaban-based regimen will be considered noninferior to the VKA-based regimen with regards to NACE, if the upper boundary of the two-sided 95% CI for hazard ratio (HR) falls below 1.38. If it is significant, then go to Step (2), otherwise stop here.
- Step (2): The Edoxaban-based regimen will be considered noninferior to the VKA-based regimen with regards to major bleeding (ISTH def.), if the upper boundary of the two-sided 95% CI for HR falls below 1.38. If it is significant, then go to Step (3), otherwise stop here.
- Step (3): The Edoxaban-based regimen will be considered superior to the VKA-based regimen with regards to major bleeding (ISTH def.), if the upper boundary of the two-sided 95% CI for HR falls below 1.00. If it is significant, then go to Step (4), otherwise stop here.
- Step (4): The Edoxaban-based regimen will be considered superior to the VKA-based regimen with regards to NACE, if the upper boundary of the two-sided 95% CI for HR falls below 1.00.

For each of the primary and secondary adjudicated endpoints, appropriate summary statistics (e.g., event rate) including 95% CI will be provided.

For each of the adjudicated endpoints, the time from reference date to the first occurrence of an event (based on CEC adjudication), is analyzed using a Cox proportional hazard model with treatment regimen as a factor and all the stratification factors from the randomization (IXRS) [dose adjustment [yes, no]] as covariates, to provide point estimates and 95% Confidence Interval (CI) for the hazard ratio (HR). Depending on the analysis period used in the statistical analysis, subjects without an occurrence of an event

will be censored at the last date of the analysis period or at the last date of known outcomes status. The latter is determined an individual basis for subjects with incomplete follow-up.

To evaluate the robustness of the primary analyses, the analyses will be repeated using the mITT and PP analysis set. In addition, the statistical results based on the following analysis periods: 'initial dose to final dose + 30 days' and 'overall study period + 30 days' will be presented and will be interpreted in a more descriptive way. Results for other combinations of analysis sets and analysis periods may be presented if considered necessary.

For time to first event analyses based, cumulative event rates over time are summarized using the Kaplan-Meier method as appropriate.

11.4.2. Analyses of the secondary exploratory endpoints

The main analyses for all secondary efficacy and safety endpoints will be based on first occurrence of an (adjudicated) endpoint during the 'overall study period' for all subjects belonging to the ITT analysis set and applying the aforementioned statistical method.

There will be no formal statistical testing for secondary exploratory endpoints. HRs, CI and p-values are provided but should be interpreted in a purely descriptive exploratory manner.

To evaluate the robustness of the main analyses, the analysis will be repeated using the mITT and PP analysis set. In addition, the statistical results based on the following analysis periods: 'initial dose to final dose + 30 days' and 'overall study period + 30 days' will be presented but should be interpreted as supportive. Results for other combinations of analysis sets and analysis periods may be presented if considered necessary.

11.4.3. Pharmacokinetic/Pharmacodynamic Analyses

11.4.3.1. Pharmacokinetic Analyses

Not applicable.

11.4.3.2. Pharmacodynamic Analyses

Not applicable.

11.4.3.3. Biomarker Analyses

A potential sub-study is possible which will have a separate analysis plan.

11.4.3.4. Pharmacogenomic Analyses

Not applicable.

11.4.4. Health Economics Outcome Research (HEOR) Analyses

For healthcare resource utilization, proportion of subjects with hospitalization, number of hospitalizations, and length of hospital stay related to cardiovascular events of protocol

interest during the study will be described using summary statistics and compared between treatments.

For the PACT-Q, the absolute PACT-Q1 item scores and change from baseline values at the 12 months (or end of treatment if earlier) will be described using summary statistics and compared between treatments. In addition, the PACT-Q2 Convenience and Treatment Satisfaction scores will be summarized at each scheduled time point (Table 17.1) and compared between treatment groups.

For the EQ-5D-5L, the absolute and change from baseline values for the five domain scores, the EQ-5D-5L index value, and the EQ VAS score will be described using summary statistics by scheduled time point and compared between treatments.

Additional details will be provided in the SAP.

11.5. Safety Analyses

All safety analyses described in this section will be based on the Safety analysis set.

11.5.1. Adverse Event Analyses

Adverse events meeting the criteria defined in Section 9.3 will be recorded in the eCRF and coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1 or newer.

Treatment-emergent adverse events (TEAEs) are defined as events which start on or after any first dose of the assigned study medication regimen or started prior to but then worsened after any first dose of the assigned study medication regimen. An AE that occurs more than 30 days after the date of the last dose of the assigned study medication regimen will not be counted as a TEAE.

TEAEs will be summarized by treatment group. The incidence of TEAEs will be presented by treatment group, by relationship to the assigned study regimen, and by severity. If more than one AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship. Frequent TEAE (reported by at least 5% of subjects in any treatment group) will be summarized by regimen group.

The incidence of death, SAEs, drug-related SAEs, and AEs leading to permanent discontinuation of the assigned study regimen will be summarized. All AEs meeting the criteria defined in Section 9.3.4 will be included in a data listing and a listing to display the coding of AEs will be prepared as well.

11.5.2. Clinical Laboratory Evaluation Analyses

The clinical laboratory evaluations for each scheduled test will be summarized descriptively by treatment regimen and visit (including changes from baseline). The baseline value is defined as the last non-missing value before first administration of study medication. In addition, descriptive statistics will also be presented for the maximum and minimum post baseline values (including changes from baseline). Shift tables (in

categories of low, normal, and high) will be provided for each treatment regimen for selected laboratory parameters. Also, the number and percentage of subjects with clinically relevant abnormal laboratory values while on study drug will be calculated for each treatment regimen for selected laboratory parameters. All abnormal laboratory values will be presented in a listing.

More details will be outlined in the SAP.

11.5.3. Vital Sign Analyses

Vital signs at each evaluation point and the change from baseline will be summarized by treatment regimen. The baseline value is defined as the last non-missing value before first administration of study medication. In addition, descriptive statistics will also be presented for the maximum and minimum post baseline values (including changes from baseline).

More details will be outlined in the SAP.

11.5.4. Physical Examination Analyses

A physical examination (Section 9.12) will be performed at the Randomization Visit, End of Treatment Visit, and the Post-treatment FU Visit. The physical examination findings will be summarized by treatment regimen based on the SAF analysis set.

More details will be outlined in the SAP.

11.5.5. Electrocardiogram Analyses

The ECG evaluations at baseline and at all post baseline visits including the FU visit will be summarized by treatment regimen based on the SAF analysis set.

More details will be outlined in the SAP.

11.6. Other Analyses

If applicable, details on other analyses will be provided in the SAP.

11.7. Interim Analyses

Not applicable.

11.8. Data and Safety Monitoring Board (DSMB)

There will be an independent DSMB to protect the rights, safety and well-being of subjects participating in this study. The DSMB will be involved in the management of this clinical study serving as the safety monitoring advisory group for the study. The primary role of the DSMB will be to examine the safety data on an ongoing manner and to alert the Executive Committee in case of any clinically concerning safety issues.

The frequency and extent of the data reviews by the DSMB, details about the reviews and stopping rules or criteria for evaluating need for study protocol modifications will be described and specified in the DSMB Charter.

11.9. Sample Size Determination

In order to determine the sample size, the following assumptions were made:

- *Event rate:* Based on published literature and results from the ENGAGE AF-TIMI 48 study, it is assumed that the event rate of the primary efficacy endpoint of NACE in AF-subjects with TAVI treated with VKA would be 14%/year.
- *Noninferiority margin*: No data were available for placebo-controlled studies in this subject population. The Executive Committee reviewed all available data including practice changes observed in other areas of cardiology on the basis of clinical trials and the level of statistical certainty they had achieved. Then it made the judgment that a noninferiority margin for hazard ratio 1.38 would be accepted by the medical community for a practice change given the fact that other trials have already supported the use of Edoxaban in subjects warranting anticoagulation and its related regulatory approval for human use in the participating countries.
- *Significance level for statistical testing*: 0.05.
- *Observed hazard ratio*: 0.95.

With the above assumptions, to demonstrate noninferiority with 80% of power, the study needs to collect at least 320 NACE across the combined study arms. With an anticipated median follow-up time of two years and an annual event rate of 14%, a total of approximately 1400 subjects need to be randomized.

The sample size is event driven. The sample size or the duration of follow-up may require adjustment based on the actual versus anticipated primary endpoint event and drop-out rates.

11.10. Statistical Process

The statistical analysis will be performed by the assigned CRO under the guidance of the Daiichi Sankyo study biostatistician.

A Statistical Analysis Plan will be written providing all the details on the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describing the approaches to be taken for summarizing other clinical study information such as, but not limited to, subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications.

To preserve the integrity of the statistical analysis and clinical study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC 27513).

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/EtC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of a clinical study. Furthermore, the Investigator/investigational site will supply the CEC with whatever information that is requested such that the CEC will be able to perform their adjudication duties.

12.1. Monitoring and Inspections

The monitor and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, source data, and other pertinent documents).

The monitor is responsible for visiting site(s) at regular intervals (as detailed in the monitoring plan) depending upon the site enrollment and monitoring needs of the site, throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. Source document verification procedure and process is addressed in the study monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories, etc.) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.2. Data Collection

This study employs electronic data capture. The eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study. The eCRF will be completed, reviewed, and electronically signed by the Investigator. Guidelines will be provided to facilitate data entry in the electronic data capture modules.

All written information, study notes, and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood as source documentation.

12.3. Data Management

All data management related tasks, responsibilities, and processes are noted in the data management plan for the study.

Each subject will be identified in the database by a unique subject identifier as defined by the Sponsor.

To ensure the quality of clinical data across all subjects and study centers, a Clinical Data Management review will be performed on subject data according to specifications given by the Sponsor or designee(s). Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the electronic data capture application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the Clinical Data Management review process, eCRF queries will be raised and resolved within the electronic data capture application.

Data received from external sources such as laboratories and IXRS will be reconciled to the clinical database.

Serious Adverse Events in the clinical database will be reconciled with the safety database.

All medical history entries (except terms pre-specified on the eCRF) and AEs will be coded using MedDRA. All prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary.

12.4. Study Documentation and Storage

The Investigator will maintain a Signature Log of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Signature List.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects, date and outcome of screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential Subject Identification Code Log. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, x-rays, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential)

documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed eCRFs, informed consent forms, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB/EtC and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study center, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

All essential documentation will be retained by the institution until told otherwise by the Sponsors.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

No study document should be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Sponsor in writing of the new responsible person and/or the new location.

All Investigators and site personnel must ensure subject confidentiality as outlined in Section 15.2 .

12.5. Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (e.g., protocol and amendments, IEC/EtC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigators and/or their Institution will sign a clinical study agreement with Daiichi Sankyo. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

CCI

[redacted]

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- European Commission Directive (2001/20/EC Apr 2001) and/or
- European Commission Directive (2005/28/EC Apr 2005) and/or
- US Food and Drug Administration GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 of 25 November, 2014
- Other applicable local regulations

15.2. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

For European Union (EU) study centers, the Sponsor will observe the rules laid down in the European Data Protection Directive 95/46/EC on the protection of individuals with regards to the processing of personal data and the free movement of such data.

The Investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (e.g., signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/EtC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The

written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EtC or IRB prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF and the subject Assent Form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

Suggested model text for the ICF for the study and any applicable subparts (PK, etc.) are provided in the Sponsor's ICF template for the Investigator to prepare the documents to be used at his or her study center. Updates to applicable forms will be communicated via letter from the Sponsor.

For studies in the US, an additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator Brochure, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (e.g., advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the EtC/IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Investigator must submit and, where necessary, obtain approval from the EtC or IRB for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the EtC/IRB of deviations from the protocol or SAEs occurring at the study center and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after approval by the relevant regulatory bodies.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Regulatory Authorities in any area of the world, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the Investigator becomes aware of.

15.5. Protocol Deviations

The Investigator shall conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority/ies, and which was given approval/favorable opinion by the IRBs/ECs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (e.g., inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least 1 administration of study drug, data should be collected for safety purposes.

- If applicable, the Investigator should notify the IRB/EtC of deviations from the protocol in accordance with local procedures.

15.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, ECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB/EtC. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by the Sponsor or the CRO. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

A global protocol amendment will affect study conduct at all study centers in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a particular study center(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB/EtC and by regulatory authorities where appropriate, unless immediate implementation of the change is necessary for subject safety.

15.8. Study Termination

The independent DSMB may recommend termination of the study. Termination may be made for any of the following reasons:

- Concern about significantly higher bleeding risk relative to one of the study arms,
- Any safety concerns based on benefit/risk evaluation.

The DSMB will alert the Investigator or designee if there are any of the above concerns requiring protocol modifications or any other changes in the study.

The details about the roles and responsibilities of the DSMB and guidelines and rules for monitoring the study safety data will be described further in the DSMB Charter.

The Sponsor has the right to terminate the study at any time for commercial (budget) reasons, delayed recruitment, subject safety, or results from other research. The study termination may also be requested by (a) competent authority(ies).

15.9. Data and Safety Monitoring Board

An independent DSMB will be created to further protect the rights, safety, and well-being of subjects who will be participating in this study by monitoring their progress and results. The DSMB will comprise of qualified scientists, who are not Investigators in the study and not otherwise directly associated with the Sponsor. The DSMB will be described in detail in the DSMB Charter. The DSMB will monitor data during the study. All activities of the DSMB will be documented. This documentation will include data summaries and analyses provided to the committee as well as minutes of the meeting. The DSMB can recommend study or treatment regimen/group termination to the Study Oversight Committee based on pre-specified concerns described in the DSMB Charter.

The documentation will remain confidential within the DSMB until the study is completed. An independent statistician who is not otherwise involved in the study will prepare the required data outputs and provide the outputs to the DSMB as per the DSMB Charter.

15.10. Clinical Events Committee

An independent study specific CEC will review and adjudicate key endpoint events as outlined in the CEC Charter.

The CEC will comprise qualified judges, who are not Investigators in the study and not otherwise directly associated with the Sponsor. The CEC judges will remain blinded to treatment throughout the adjudication process and the study. The CEC-adjudicated data will be used in the final efficacy and safety analyses. The CEC and the events it will adjudicate will be detailed in the CEC Charter.

The Investigator/investigational site will supply the CEC with whatever information that is requested such that the CEC will be able to perform their adjudication duties.

15.11. Executive Committee

The Executive Committee will be responsible for the overall design, conduct, and supervision of the study, including the development of any protocol amendments. The Executive Committee will also review the progress of the study at regular intervals to ensure subject safety and study integrity. The Executive Committee will be composed of designated representatives from the CRO and Sponsor.

15.12. Steering Committee

A study Steering Committee will include the Executive Committee members and National Lead Investigators and will be responsible for supporting the Executive Committee in making strategic decisions for the study, working with the Executive Committee to provide overall oversight for the trial, and enhancing the study implementation to optimize the quality of the data and study integrity.

15.13. Operations Committee

A, optional Operational Committee will be responsible for the ongoing monitoring of the study data and implementation of steps to improve the quality of the study conduct. The Operational Committee will be comprised of designated representatives of CROs and Sponsor and will report at regular intervals to the Executive Committee on the progress of the study.

15.14. Sub-studies

Subjects in this study may participate in one or more sub-studies. Dedicated sites are invited for participation according to sites capabilities to meet specific sub-studies requirements and on the required number of observations. Currently, sub-studies are being considered involving:

- Parameters of hemostasis such as WBCT, TEG, and MEA.

15.15. Address List

A list of key study personnel (including personnel at the Sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and updated in study reference materials.

16. REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. Lancet 2006; 368:1005-11.
2. Otto CM, Prendergast B. Aortic-valve stenosis - from patients at risk to severe valve obstruction. NEJM 2014; 371:744-56.
3. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. NEJM 2011; 364:2187-98.
4. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. NEJM 2010; 363:1597-607.
5. Yousef A, MacDonald Z, Simard T, et al. Transcatheter aortic valve implantation (TAVI) for native aortic valve regurgitation- a systematic review. Circ J 2018; 82(3): 895-902.
6. Silaschi M, Conradi L, Wendler O, Schlingloff F, et al. The JUPITER registry: One-year outcomes of transapical aortic valve implantation using a second generation transcatheter heart valve for aortic regurgitation. Catheter Cardiovasc Intery 2018; 91(7): 1345-51.
7. Lindman BR, Pibarot P, Arnold SV, et al. Transcatheter versus surgical aortic valve replacement in patients with diabetes and severe aortic stenosis at high risk for surgery: an analysis of the PARTNER Trial (Placement of Aortic Transcatheter Valve). JACC 2014; 63:1090-9.
8. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. JACC 2014; 63:1972-81.
9. Rodés-Cabau J, Dauerman H, Cohen M, et al. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. JACC 2013; 25:2349-59.
10. Rigshospitalet, Denmark. Comparison of transcatheter versus surgical aortic valve replacement in younger low surgical risk patients with severe aortic stenosis (NOTION-2). ClinicalTrials.gov Identifier: NCT02825134
11. Généreux P, Cohen D, Mack M, et al. Incidence, Predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement. JACC 2014; 64: 2605-15.
12. Rodés-Cabau J, Dauerman HL, Cohen MG, et al. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. JACC 2013; 62:2349-59.
13. Ussia GP, Scarabelli M, Mulè M, et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. Am J Cardiol 2011; 108:1772-6.

14. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. NEJM 2012; 366:1686-95.

15. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. NEJM 2012; 366:1696-704.

16. Holmes DR, Jr., Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. JACC 2012; 59:1200-54.

17. Durand E, Blanchard D, Chassaing S, et al. Comparison of two antiplatelet therapy strategies in patients undergoing transcatheter aortic valve implantation. Am J Cardiol 2014; 113:355-60.

18. Webb J, Rodés-Cabau J, Fremes S, et al. Transcatheter aortic valve implantation: a Canadian Cardiovascular Society position statement. Can J Cardiol 2012; 28:520-8.

19. Holmes DR, Jr., Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement: developed in collaboration with the American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Mended Hearts, Society of Cardiovascular Anesthesiologists, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. The Journal of Thoracic and Cardiovascular Surgery 2012; 144:e29-84.

20. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013; 381:1107-15.

21. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. NEJM 2013; 369:2093-104.

22. Hokusai VTE Investigators, Büller HR, Décousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. NEJM 2013; 369:1406-15.

23. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve, replacement in intermediate-risk patients. NEJM 2016; 374:1609-20.

24. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. NEJM 2011; 364:2187-98.

25. Leon MB, Smith CR, Mack M. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. NEJM 2010; 363:1597-1607

26. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993; 69:236-239.

27. Schulman S, Kearon C, and Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692-4.

28. Mehran R, Rao SV, Bhatt DL, Gibson CM, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011; 123:2736-47.

29. Topol E, et al. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. NEJM 1993; 329:673-82

30. Mylotte D, Piazza N. Transcatheter aortic valve replacement failure: déjà-vu ou jamais vu? Circ Cardiovasc Interv 2015; 8: e002531

17. APPENDICES

Table 17.1: Table of Events of Treatment Period

Visit Number		**1**	**2***	**3***	**4***	**5***	**6***	**7***	**8***	**9***	**10**
Visit timing	**Screening**	**Baseline/ran-domization (DAY 1)**	**3 M ±14d**	**6 M ±14d**	**12M ±14d**	**18M ±14d**	**24M ±14d**	**30M ±14d**	**EOT[l, m] 36 M ±14d**	**Post treatment Follow-up 1 M post EOT ± 7d**	**Follow-up contact** (every 6±1 months after EOT)[p]
Study informed consent[a]	***x***										
Inclusion/Exclusion Criteria	***x***										
Record EuroSCORE 1 and 2, STS elements and CHAD and HAS-Bleed scores in eCRF		***x***									
Check local lab results[b]	***x***										
Demographic information	***x***										
Medical/surgical history (including bleeding and for the past 30 days, medication history)	***x***	***x***									
Contact IXRS	***x***	***x***[c]									
Administer first study dose of OAC[d]		***x***									
Dispense assigned OAC[e]		***x***	***x***	***x***	***x***	***x***	***x***	***x***	**NA**	**NA**	
Collect unused medication									**x**		
Concomitant medication			***x***	***x***	***x***	***x***	***x***	***x***	**x**	**x**	**x**
Physical examination		***x***							**x**	**x**	
Vital signs[f]		***x***	***x***	***x***	***x***	***x***	***x***	***x***	***x***	***x***	

Visit Number		**1**	**2***	**3***	**4***	**5***	**6***	**7***	**8***	**9***	**10**
Visit timing	**Screening**	**Baseline/ran-domization (DAY 1)**	**3 M ±14d**	**6 M ±14d**	**12M ±14d**	**18M ±14d**	**24M ±14d**	**30M ±14d**	**EOT[l, m] 36 M ±14d**	**Post treatment Follow-up 1 M post EOT ± 7d**	**Follow-up contact** (every 6±1 months after EOT)[p]
12-lead ECG[g]		***x***							***x***		
Blood draw[h], INR recording		***x***[b]	***x***	***x***	***x***	***x***	***x***	***x***	***x***	***x***	
PACT-Q1, Q2 and EQ-5D-5L[i]		**x**	***x***		***x***				***x***		
Review study regimen compliance & interruptions[j]			***x***	***x***	***x***	***x***	***x***	***x***	***x***	**NA**	
Assessment and recording of (S)AEs and suspected clinical events including hospitalizations[k]		***x***	***x***	***x***	***x***	***x***	***x***	***x***	***x***	***x***	***x***
Transition to open-label medication[l]									***x***		
Notify study team in case TTE or TEE or CT were performed as part of routine care and record parameters.		***x***	***x***	***x***	***x***	***x***	***x***	***x***	***x***	**NA**	
Serum pregnancy test[n]	***x***										
Urine pregnancy test[o]			***x***		***x***		***x***		***x***	***x***	

Abbreviations: AE = adverse event; CBC= complete blood count; CrCL = creatinine clearance; CRO = clinical research organization; CT = computer tomography; d = day(s); ECG = electrocardiogram; echo = echocardiogram; eCRF = electronic case report form; EQ-5D-5L = EuroQuality of Life (EQ-5D-5L) Questionnaire; EOT = end of treatment; INR = international normalized ratio; IXRS = interactive web/voice response system; M = month(s); NA = not applicable; PACT-Q = Perception of Anticoagulant Treatment Questionnaire; OAC = oral anticoagulant; OAP = oral antiplatelet; SAE = serious AE; STS = Society of Thoracic Surgeons; TEE = transesophageal echo; TTE = transthoracic echo; ULN = upper limit of normal; VKA = Vitamin K antagonist.

* Visits may be on-site or at the subject's current place of living, but must be conducted by the investigator or appropriately trained designee (see Section 6.4).

a Subjects eligible to participate in the study provide written IC before randomization or any study-specific procedures. Once written IC is obtained, subject should be randomized without delay.

b Check the most recent results from local laboratory tests done within the 15 days before randomization against the exclusion criteria. Creatinine and CBC must be available from blood draws after TAVI with the subject being clinically stable. CrCL should be calculated by the Cockcroft-Gault formula as described in Section 17.7 and the results should be available at each study visit in time to determine correct dosing for Edoxaban subjects.

c Contact IXRS for randomization and pre-declaration of oral antiplatelet therapy by drug, dose, and projected last dose if applicable. Also contact IXRS for change in Edoxaban dosing, and prior to any distribution of Edoxaban; the end of Edoxaban treatment also needs to be recorded in IXRS.

d First dose should be should be administered within the 5 days after TAVI (in case of pacemaker deployment within the 7days after TAVI) but within 24 hours of randomization; however, NO EARLIER than the morning after successful TAVI. For suggested starting dosing see Section 5.2.1.1.1 and Section 5.2.1.2.1. Predefine and institute OAP (see Section 3.1).

e Daiichi Sankyo supplies study subjects with Edoxaban. VKA and OAP will be provided or prescribed by the site through the hospital or a physician. See Section 3.1 about OAP administration.

f Vital signs include sitting blood pressure and heart rate; body temperature, weight, and height. Height only needs to be recorded at randomization.

g If 12-lead ECG medically necessary and obtained at any other time, the results need to be recorded.

h Obtain blood samples for analysis of hematology and blood chemistry by a local certified/accredited laboratory (see Section 9.9). Creatinine and CBC must be available from blood draws after TAVI with the patient being clinically stable. CrCL should be calculated by the Cockcroft-Gault formula. Normal lab ranges also need to be documented within the eCRF. For Visits 2 and onward. If recent (within 15 days before randomization) lab values for blood analyses are available through standard of care, these values may be reported and no new sampling or analyses is required.
VKA subjects only: INR values and VKA dose are collected (preferably monthly) and entered into the eCRF either during the study visits by local lab determination (if they haven't already been entered). INR values and VKA doses collected through the general practitioner, a local anticoagulation clinic, or by the trained and certified patient using a certified device must also be considered and collected. However, this does not constitute a waiver for subject's planned INR determination during study visits. Dose of VKA may need to be adjusted based on these results to maintain INR values from 2.0 to 3.0 (numbers inclusive) [Japan: 1.6-2.6 in subjects age ≥70 (numbers inclusive)].***Liver function panel will be obtained at Screening (unless recent, within the last 15 days, results are available), and at the 6 and 12 Month Visits, unless clinically necessary at other time points.***

i PACT-Q1 and EQ-5D-5L at Randomization, PACT-Q2 and EQ-5D-5L at 3 months and again at either 12 months or at EOT, whichever comes first. Forms will be collected by the CRO for uploading into the data system.

j Antithrombotic regimen compliance is evaluated at each visit/telephone assessment (both by pill count, self-reporting/physician-reporting, subject medication log, and for VKA subjects only, by INR values). In case of a suspected study endpoint, an additional assessment for subject compliance to the assigned regimen must be performed.

k Assessment and recording of (S)AEs and suspected clinical events from the signing of the informed consent, and should be reported as soon as site personnel learn of the event and be reported within 24h of the Investigator's/site's awareness. Endpoint event and AE reporting should occur throughout the study and not be restricted to specific visits. If AST or ALT > 3xULN with simultaneous total bilirubin levels > 2xULN is observed, then ALP should be determined. Hospitalization due to cardiovascular events needs to be assessed.

l When subjects are being transitioned to non-study medications, record the date and time of last administration of study medication, and collect all unused study medication. Subjects are transitioned to an approved OAC of the Investigator's or treating physician's choice. The Investigator will follow the transition strategy in the approved product label. Subjects who prematurely discontinue study OAC are requested to also complete the Post-treatment Follow-up Visit according to this schedule (See Section 5.2.1.1.2 and Section 5.2.1.2.2).

m EOT may occur at any time (e.g., at subject withdrawal or discontinuation) and will trigger this subject's Post-treatment Follow-up Visit.
n Female subject who are of child bearing potential.
o Female subject who are of child bearing potential. Furthermore, pregnancy tests are carried out whenever there are clinical indications for the existence of a pregnancy.
p All subjects who have taken study medication should be requested to consent for routine follow-up contact at 6-month intervals following termination of study drug. This will normally be as a phone contact until the end of the study is determined by the Sponsor. Should the subject choose to not receive phone calls, the site may attempt to retrieve this information from viewing the subject's medical records or public records.

17.1. Bleeding Criteria

17.1.1. ISTH Bleeding Criteria

Table 17.2: ISTH Bleeding Criteria[27]

ISTH Bleeding Criteria
Major bleeding • Clinically overt bleeding that is associated with: o A fall in hemoglobin of 2 g/dL (1.24 mmol/L) or more, or o A transfusion of 2 or more units of whole blood or packed red blood cells, or o Symptomatic bleeding in a critical site or organ such as: intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intra-articular, intramuscular with compartment syndrome, or o A fatal outcome
Clinically relevant non-major (CRNM) bleeding • Any sign or symptom 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 the ISTH definition of major bleeding but does meet at least one of the following criteria: o requiring medical intervention by a healthcare professional o leading to hospitalization or increased level of care o prompting a face to face (i.e., not just a telephone or electronic communication) evaluation. **Minor** • Bleeding episodes not requiring any medical attention and therefore not meeting the criteria for major or clinically relevant non-major bleeding.

17.1.1.1. Definitions of terms

Abnormal liver function is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin > 2 X the ULN, in association with aspartate aminotransferase/alanine transferase > 3 X the upper limit of normal).
Abnormal renal function is defined as chronic dialysis, renal transplantation, or serum creatinine ≥ 200 µmol/L (≥ 2.26 mg/dL).

Congestive heart failure is defined as the current presence or prior history of clinical congestive heart requiring medical attention and medical therapy or documented Ejection Fraction ≤ 35% (left ventricular systolic dysfunction).
Diabetes Mellitus includes diabetes requiring treatment with diet only or with pharmacologic therapy (insulin, oral hypoglycemic agents).
Documented clinical need is defined as a known record in any form (incl. written, electronic or verbal) recording pertinent subject data with regards to the clinical reason for the choice of an alternative medication. This reason must be captured and pre-declared before subject randomization.
Labile INRs is defined as unstable or high INRs or poor time in therapeutic range (e.g., < 60%) while on a Vitamin K antagonist.
Hypertension is defined as hypertension requiring pharmacologic therapy to maintain a BP < 140/85 mmHg or untreated hypertension documented by BP > 140 mmHg systolic or > 90 mmHg diastolic on two separate occasions.
Stroke: Stroke is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit that is generally in the distribution of a single brain artery (including the retinal artery) and that is not due to an identifiable non-vascular cause (i.e., brain tumor or trauma). The deficit must either be associated with symptoms lasting more than 24 hours or result in death within 24 hours of symptom onset.
TIA: TIA is defined as an abrupt onset, over minutes to hours, of a focal non-fatal, neurological deficit in the distribution of a single brain artery (including the retinal artery) that lasts less than 24 hours and that does not satisfy the definition of stroke above.

17.1.2. TIMI (Non-CABG)

- Major
  - Any intracranial hemorrhage or any clinically overt bleeding, (including bleeding evident in imaging studies) associated with a fall of hemoglobin (Hb) of ≥ 5g/dL
  - Fatal bleed
- Requiring Medical Attention
  - Overt sign of hemorrhage not meeting major or minor bleed
  - Requiring intervention
  - Leading to or prolonging hospitalization
  - Prompting evaluation

- Minor
    - Any clinically overt bleeding associated with a fall in Hb ≥ 3g/dL but < 5 g/dL
- Minimal
    - Any clinically overt bleeding associated with a fall in Hb <3g/dL

17.1.3. BARC Bleed Scoring[28]

Type 0: no evidence of 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 healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare 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 type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3: clinical, laboratory, and/or imaging evidence of bleeding with healthcare provider responses

- **Type 3a:** any transfusion with overt bleeding; overt bleeding plus Hb drop of 3 to < 5 g/dL (provided Hb drop is related to bleed)
- **Type 3b:** overt bleeding plus Hb drop ≥ 5 g/dL (provided Hb drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive drugs
- **Type 3c:** intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision

- **Type 4**: coronary artery bypass graft (CABG)-related bleeding
    - Perioperative intracranial hemorrhage within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of ≥ 5 U whole blood or packed red blood cells within 48-hour period; chest tube output 2 L within a 24-hour period
- Notes: 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 but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

- **Type 5**: fatal bleeding
    - Type 5a: probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
    - Type 5b: definite fatal bleeding; overt bleeding or autopsy or imaging confirmation
- BARC fatal bleeding is meant to capture deaths that are directly due to bleeding with no other cause. The time interval from bleeding event to death should be considered with respect to likely causality, but there is no specific time limit proposed.

17.1.4. GUSTO Definitions[29]

- Severe or life-threatening
    - Intracerebral hemorrhage
    - Resulting in substantial hemodynamic compromise requiring treatment
- Moderate
    - Requiring blood transfusion but not resulting in hemodynamic compromise
- Mild
    - Bleeding not meeting the criteria of moderate or severe

17.2. Myocardial Infarction (Varac-2 & ESC/Third Universal)

Table 17.3: Myocardial Infarction (MI) According to the VARC-2 Definitions

Peri-procedural MI (< 72 hours 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 (preferably CK-MB) within 72 hours 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 (> 72 hours 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 99th percentile URL, together with the evidence of myocardial ischemia with at least one of the following: o 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
- 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.

Table 17.4: Myocardial Infarction (MI) According to the ESC Criteria/Third Universal Definition

Type	
1	Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe coronary artery disease (CAD) but on occasion non-obstructive or no CAD. Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac Troponin (cTn)) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: • Symptoms of ischemia • (Presumed) new significant ST-T wave changes or new left bundle branch block (LBBB) • Development of pathological Q waves • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality • Identification of an intracoronary thrombus by angiography or autopsy
2	In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH. Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac Troponin (cTn)) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: • Symptoms of ischemia • (Presumed) new significant ST-T wave changes or new LBBB • Development of pathological Q waves • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Type	
	Identification of an intracoronary thrombus by angiography or autopsy
3	Cardiac death with symptoms suggestive of MI and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased
4a	Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 X 99th percentile URL) in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
4b	Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
5	Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 X 99th percentile URL) in patients with normal baseline cTn values (≤ 99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

17.3. Cerebrovascular event

Stroke is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit that is generally in the distribution of a single brain artery (including the retinal artery) and that is not due to an identifiable non-vascular cause (i.e., brain tumor or trauma). The deficit must either be associated with symptoms lasting more than 24 hours or result in death within 24 hours of symptom onset.

TIA is defined as an abrupt onset, over minutes to hours, of a focal non-fatal, neurological deficit in the distribution of a single brain artery (including the retinal artery) that lasts less than 24 hours and that does not satisfy the definition of stroke above.

17.3.1. Stroke is classified according to the VARC-2 definitions.

Diagnostic criteria

- 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

• 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 • No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, 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 Note: 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).
** **Determination of "Disabling/non-disabling stroke" will not be part of adjudication assessment**

17.3.2. ECASS I Criteria [European Cooperative Acute Stroke Study (ECASS)

Type	Definition
HI1	Small petechiae along the margin of the infarct
HI2	More confluent petechiae within the infarct but without space-occupying effect
PH1	Blood clot not exceeding 30% of the infarct area with some mild space-occupying effect
PH2	Blood clots exceeding 30% of the infarct area with significant space-occupying effect

17.4. Valve thrombosis

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.

17.4.1. Assessment of the occurrence of bioprosthetic valve thrombosis is based on Mylotte:[30]

i. presence of progressive dyspnea or heart failure worsening;
ii. increase in transaortic mean gradient by ≥ 10 mm Hg, a transaortic mean gradient of ≥ 20 mm Hg, thickening of heart valve leaflet (HALT) with impaired mobility (HAM) or visualization of thrombus formation on the valve;
iii. visualization of thrombus formation by cardiac computed tomography scan;
iv. complete reversibility after high intensity anticoagulation (e.g., IV heparin).

17.5. Systemic thromboembolism

Systemic thromboembolism [non-central nervous system] 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.

17.6. User Guide for EQ-5D-5L

EQ-5D-5L User Guide. Basic information on how to use the EQ-5D-5L instrument. http://www.euroqol.org/about-eq-5d/publications/user-guide.html

17.7. Calculation of Creatinine Clearance (CrCL)

The Cockcroft-Gault formula for the calculation of CrCL will be used in this study.

Creatinine Clearance for Males:

CrCL = [140 – age (years)] x [body weight (kg)] / [72 x serum creatinine (mg/dL)]

Creatinine Clearance for Females:

CrCL = 0.85 x [140 – age (years)] x [body weight (kg)] / [72 x serum creatinine (mg/dL)]