CLINICAL STUDY PROTOCOL

EVALUATION OF THE SAFETY AND EFFICACY OF AN EDOXABAN-BASED COMPARED TO A VITAMIN K ANTAGONIST-BASED ANTITHROMBOTIC REGIMEN F0 bb0 WING-SYGGESFUb- ERGU+ ANEQU S- CORONARY INTERVENTION (PCI) WITH STENT PLACEMENT. IBDOXABAN TREATMENT VERSUS VKA IN PATIENTS WITH AF UNDERGOING PCI- ENTRUST- AF PCI)

DSE-ED0-01-15-EU

EudraCT NUMBER 2016-002683-14

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INVESTIGATOR AGREEMENT

Evaluation of the safety and efficacy of an edoxabc1n-based compared to a vitamin K antagonist-based antithrombotic regimen following successful percutaneous coronary intervention (PCI) with stent placement. (EDOXABAN TREATMENT VERSUS VKA IN PAIIENTS WITH AF UNDERGOING PCI - ENTRUST AF-PCI).

Investigator's Signature:

I have fuliy 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 con iderations and guidelines, and to conduct the studyin accordance with the Declaration of Helsinki, International Conference on Harmonization guidelines on Good Clinical Practice (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.

Date	**Signature**
Site no.	**Investigator'sname and address (print or stamp)**

Spollijor Appl'oval:

This clinical study protocol hasbeen re`ewedand approved by:

Signatur [redacted] Date 07 - March - 2017

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Draft 03 17
Not filled out

[redacted]

PROTOCOL SYNOPSIS

EudraCT Number:	2016-002683-14
Protocol Number:	DSE-EDO-01-15-EU
Investigational Product:	Edoxaban (DU-176b)
Active Ingredient(s)/ international non-proprietary name:	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.:	Evaluation of the safety and efficacy of an edoxaban-based compared to a vitamin K antagonist-based antithrombotic regimen following successful percutaneous coronary intervention (PCI) with stent placement. IBdoxabaN Treatment vers!!§. VKA in pa!ients with **AF** undergoing **PCI** (ENTRUST-AF PCI)
Study Phase:	Phase 3b
Indication Under Investigation:	Subjects with atrial fibrillation (AF) following successful PCI with stent placement.
Study Objectiyes:	The **primary objective** is to compare a 12-month antithrombotic regimen of edoxaban in combination with clopidogrel or another P2Y12 antagonist against a regimen of a vitamin K antagonist (VKA) in combination with clopidogrel or another P2Y12 antagonist and 1-12 months ASA in subjects with AF following successful PCI with stent placement in terms of the incidence of major or clinically relevant non-major ISTH-defined bleeding (MCRB). There are two primary hypotheses for bleeding to be tested consecutively in this study. • The edoxaban-based antithrombotic regimen is non-inferior to the VKA-based antithrombotic regimen with regards to MCRB. • The edoxaban-based aritithrombotic regimen is superior to the VKA-based antithrombotic regimen with regards to MCRB.

These two hypotheses are tested in a hierarchical mariner, non-: inferiority followed by superiority to control the type-I error rate, with adequate power for each of the two hypotheses.

Secondary exploratory objectives of the study are to compare the edoxaban-based antithrombotic regimen to the VKA-based antithrombotic regimen with regard to:

- Main efficacy endpoint (MEE), defined as the composite of cardiovascular (CV) death, stroke, systemic embolic events (SEE), spontaneous myocardial infarction (MI) and definite stent thrombosis.
- Net clinical benefit (NCB), defined as the composite of CV death, stroke, SEE, spontaneous MI, definite stent thrombosis and ISTH-defined major bleeding.
- Main thromboembolic event, defined as composite of cardiac or thromboembolic death (thromboembolic death considered to be thromboembolic in Ofigin (including thromboembolic stroke, pulmonary embolism, any other systemic embolism), ischemic stroke, SEE, spontaneous MI and definite stent thrombosis.
- ISTH-defined major bleeding
- Any bleeding defined as the composite of major, clinically relevant non-major and minor bleeding (ISTH definition)
- Symptomatic intracranial hemorrhage (ICH)
- Composite of stroke and SEE
- Composite of all-cause death, stroke, SEE, spontaneous MI and definite stent thrombosis
- Composite of CV death, spontaneous MI and definite stent thrombosis
- The single components of the composite primary and secondary endpoints mentioned above are explored.
- Safety parameters such as (serious) adverse events, laboratory parameters, ECG and vital signs.

Study Design:	This is a multinational, multicenter, randomized, open-label Phase 3b study with blinded evaluation of endpoints by an independent Clinical Event Committee (CEC) [PROBE design]. An

independent Data and Safety Monitoring Board (DSMB) is responsible for monitoring safety during the study.

Subjects eligible to participate in the study provide written informed consent (IC) before randomization or any study-specific procedures. Once written IC is obtained, subject should be randomized without delay via an interactive voice and web response system (IXRSJ.

The Investigator should be prepared to provide subject information, including, but not limited to: age, body weight, clinical presentation (ACS or stable coronary disease), CrCL using Cockcroft-Gault formula and CKD-EPI Equation for estimating GFR on the Natural Scale (see Section 17.6) and whether the subject is taking certain concomitant P-gp inhibitors (see Section 5.3.1).

Randomization is stratified by clinical presentation (ACS or stable coronary disease), requirement for dose adjustment of edoxaban (60 or 30 mg), and geographical region. Subjects are assigned randomly via the above mentioned IXRS such that the study has a I: I ratio of subjects in the two antithrombotic treatment regimens:

- Edoxaban-based regimen for 12 months:
    1. Edoxaban 60 mg once-daily or 30 mg once-daily in selected subjects (see below "Dosage Form, Dose, and Route of Administration"and Section 5.3.1).
    2. Clopidogrel 75mg once-daily (or in the presence of a documented clinical need prasugrel [5mg or 10 mg once-daily] / ticagrelor [90 mg twice-daily] may be used).

       The use of a $P2Y_{12}$ antagonist other than clopidogrel must be pre-declared.
    3. Concomitant use of another anti-platelet agent (i.e. ASA) is **not** allowed.

- VKA-based reg11I1en for 12 months:
    1. The VKA of choice with once-daily dosing for target international normalized ratio (INR) between 2.0 to 3.0, inclusive.
    2. Clopidogrel 75mg once-daily (or in the presence of a documented clinical need prasugrel [5mg or 10 mg once-daily] / ticagrelor [90 mg twice-daily] may be used).

	3. ASA (100 mg once-daily) for a minimum of 1 month and up to 12 months duration at the Investigator discretion guided by the clinical presentation (ACS or stable coronary disease), and upon the CHA2DS2-VASc and HAS-BLED score. (1} 4. If the use of a P2Y12 antagonist other than clopidogrel must be pre-declared, together with the intended duration of ASA treatment. All dosage adjustments are implemented through the IXRS. The IXRS provides the appropriate drug supply kit number based on the subject's information as provided by the Investigator. Note: For simplicity, this protocol uses the term "edoxaban" to refer to edoxaban tosylate, "clopidogrel" to refer to clopidogrel bisulfate and the term " prasugrel" to refer to prasugrel hydrochloride.
Study Duration:	The assigned regimens (edoxaban-based or VKA-based) are continued for 12 months and all subjects are followed for 12 months irrespective of permanent or temporary changes in the antithrombotic regimen. Clinical follow-up is only terminated at the explicit documented request of the subject. All subjects on edoxaban or VKA at 12 months, have a contact planned 30 days after the end-of-treatment (EOT) visit, to collect data on targeted concomitant medications, SAEs, and other safety events of interest. The overall duration of subject participation from screening through follow-up is therefore approx. 13 months.
Study Sites and Location:	It is planned to enroll 1500 subjects (750 per antithrombotic regimen) in at least 150 study sites in Europe, and Asia-Pacific.
Subject Eligibility Criteria:	OAC indication for atrial fibrillation for a period of at least 12 months following successful PCI with stenting in adult male and female patients ?:18 years of age. Eligibility of pre-screened subjects is assessed 4 hours after sheath removal and within 5 days after successful PCI. If a staged PCI is planned, eligibility is assessed after completion of the last stage. A *clinically successful PCI* requires both anatomic and procedural success along with relief of signs and/or symptoms of myocardial ischemia at the time of randomization (for details see Section 4.1.1).

Subjects who meet any of the following criteria are ineligible for the study:

Bleeding risks or systemic conditions

1. Known bleeding diathesis, including but not limited to,
    a. Uncontrolled active bleeding, encompassing both ISTH major and clinically relevant non-major bleeding, at the time of randomization.
    b. Lesion or condition, if considered to be a significant risk for major bleeding.

    This may include but is not limited to: unresolved gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding (e.g. malignancies with l:Iletastasis), recent unresolved brain or spinal injury, recent brain, spinal or ophthalmic surgery, any intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms (of more than 3.5 cm) or major intraspinal or intracerebral vascular abnormalities.

Medication-related

2. INR > 2.5 (the subject can be reconsidered at a later point in time, but within 5 days of sheath removal).
3. Contraindication to edoxaban, VKA, ASA and/or $P2Y_{12}$ antagonists;
4. Concomitant treatment with other antithrombotic agents, fibrinolytic therapy and chronic nonsteroidal anti-inflammatory drugs (NSAIDs).

Concomitant conditions and therapies

5. Critically ill or hemodynamically unstable subjects (at the time of randomization) including:
    a. cardiogenic shock or acute decompensated heart failure, with the requirement for vasopressor agents or inotropic support or mechanical support to support circulation
    b. respiratory failure requiring endotracheal intubation and mechanical ventilation.
6. Any prior mechanjcal valvular prosthesis;

7. Ptanned coronary or vascular intervention or major surgery within 12 months; Randomization must be deferred to the last stage in a multistep, multivessel PCI procedure;
8. Moderate or severe mitral stenosis;
9. Ischemic stroke within 2 weeks prior to randomization;
10. Uncontrolled severe hypertensionwith a systelic bloed pressure (BP) 2:180 mmHg and/or diastolic BP 2:120 mmHg;
11. End stage renal disease (ESRD) (CrCL < 15 mL/min) or on dialysis;
12. Known abnormal liver function prior to randomization (incl. hepatic disease or biochemical evidence of significant liver derangement known prior to randomization) (see appendix 17.4).

Other exclusion criteria

13. Any of the following abnormal local laboratory results prior to randomization:
    a. Platelet count< 50 x10^9/L
    b. Hemoglobin < 8 g/dL
14. Unable to provide written informed consent (IC);
15. Female subjects of childbearing potential without using highly effective contraception (female of childbearing potential is defined as one who has not been postmenopausal for at least one year, or has not been surgically sterilised, or has not had a hysterectomy at least three months prior to the start o(this study). Femal s taking oral contraceptives should have been on therapy for at least three months. Adequate contraceptives include: 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; sexual abs inence
16. Pregnant or breast-feeding subjects;
17. Assessment that the subject is not likely to comply with the study procedures or have complete follow-up;

	I8. Currently participating in another clinical trial that potentially interferes with the current study; 19. Previous randomization in th isstudy; 20. Active on prescription drug abuse and addiction; abuse of illicit substances (i.e. marijuana, cocaine, methamphetamine, heroin) and alcohol abuses during the last 12 months according to the judgement of the investigator 21. Life expectancy < 12 months.
Dosage Form, Dose, and Route of Administration:	Edoxaban: 60, 30 and 15 mg provided as film coated tablets for oral use. Subjects receive 60 mg edoxaban once-daily. A dose reduction (30 mg edoxaban once-daily) is determined for subjects with one or more of the following factors: • Moderate or severe renal impairment (CrCL 15 - 50 mL/min) • Low body weight :S 60 kg (132 lbs), • Concurrent use of P-gp inhibitors (please refer to local summary of product characteristics [SmPC] or to the Investigator Brochure [IB], as applicable); In EU countries, according to SmPC concomitant use of edoxaban with cyclosporine, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once-daily. Concomitant use of edoxaban with guinidine, verapamil, or amiodarone does not require dose reduction. For low body weight (:S.60 kg) present at randomization, the edoxaban dose is reduced permanently a,nd even if the subject gains weight, the edoxaban dose remains reduced. The dose of edoxaban returns to the regular dosage regimen of 60 mg once-daily any time the subject no longer displays any of the other above mentioned factors. After randomization and in subjects without dose reduction, if subject's: body weight drops to :S 60 kg and the body weight change is> 10% of the subject's baseline body weight, then the

edoxaban dose is reduced (i.e. to 30 mg once-daily) permanently.

CrCL becomes 15 to 50 mL/min and the CrCL change is > 20% of the subject's baseline CrCL, then the edoxaban dose is reduced.

- Develops the need for concomitant treatment with P-gp inhibitors (except quinidine, verapamil or amiodarone), then the edoxaban dose is reduced (i.e. to 30 mg once-daily).

The dose of 15 mg edoxaban once-daily is not indicated as monotherapy and is solely provided as part of transition from edoxaban 30 mg at the end of study (see Section 5.3.3).

VKA: Oral VKA of choice, as pre-defined per country, with once-daily dosing for target INR between 2.0 to 3.0, inclusive.

VKA is supplied as commercially available tablets of the preferred VKA for each selected country participating in the study, being either:

- Warfarin: 1 and 2.5 mg tablets.
- Phenprocoumon: 3 mg tablets.
- Fluindione: 20 mg tablets (exclusive to France).
- Acenocoumarol: 4 mg tablets.

The Investigator monitors the INR and adjusts the VKA dose to maintain the INR within target. It is the Investigators responsibility to collect monthly INR assessments and record these throughout the study.

$P2Y_{12}$ antagonist:

- Clopidogrel 75 mg, oral commercially available tablets.

Subjects receive clopidogrel 75 mg once-daily according to the prescribing information, or in the presence of a documented clinical need (e.g. but not restricted to known dopidogrel non-responder), either

  - Prasugrel 5 or 10 mg, oral commercially available tablets.

	Subjects receive prasugrel 10 mg once-daily or prasugrel 5 rrig once-da ly if 2: 75 years of age or :S 60 kg (132 lb), according to the prescribing information. o Ticagrelor 90 mg, oral commercially available tablets. Subjects receive ticagrelor 90 mg twice-daily according to the prescribing information. lsalicylic acid (ASA): 100 mg, oral commercially available tablets. Subjects assigned to t}J.e VKA-based regimen receive 100 mg once-daily of ASA. In subjects assigned to the edoxaban-based regimen ASA is not allowed. Sponsor supplies participating sites with study medication, consisting of edoxaban, VKA (country pre-defined), P2Y12 antagonist (clopidogrel, prasugrel or ticagrelor), and ASA. Please refer to the local SmPC or IB for edoxaban as applicable and to the SmPC of each other study medication. All dosage adjustments are implemented through the IXRS. The IXRS provides the appropriate drug supply kit number based on the subject's information as provided by the Investigator.
Study Endpoints:	Primary endpoint: The primary endpoint is the composite of major or clinically relevant non-major bleeding (MCRB) defined according to the ISTH .bleeding definitions, analyzed as time to first occurrence of any component. Secondary endpoints are defined as: Main efficacy endpoint (MEE), defined as the composite of cardiovascular (CV) death, stroke, systemic embolic events (SEE), spontaneous myocardial infarction (MI) and definite stent thrombosis (as per ARC consensus definitions). - Net clinical benefit (NCB), defined as the composite of CV death, stroke, SEE, spontaneous MI, definite stent thrombosis and ISTH-defined major bleeding. - Main thromboembolic event, defined as composite of cardiac or thromboemboiic death (thromboembolic death considered to be thromboembolic in origin(including thromboembolic stroke, pulmonary embolism, any other

	systemic embolism), ischemic stroke, SEE, spontaneous MI and definite stent thrombosis. - ISTH-defined major bleeding - Any bleeding defined as the composite of major, clinically relevant non-major and minor bleeding (ISTH definition) - Symptomatic intracranial hemorrhage.OGH) Composite of stroke and SEE Composite of all-cause death, stroke, SEE, spontaneous MI . and definite stent thrombosis Composite of CV death, spontaneous MI and definite stent thrombosis - The single components of the composite primary and secondary endpoints P1entioned above are explored, as well as specific subcategories (e.g., hemorrhagic, ischemic and undetermined stroke) Safety parameters such as (serious) adverse events, laboratory parameters, ECG and vital signs. All secondary endpoints are analyzed as time to first occurrence of any of its components. Bleeding events are also classified according to Bleeding Academic Research Consortium (BARC) and Thrombolysis in Myocardial Infarction (TIMI) classifications for descriptive purposes only. All suspected bleeding events are adjudicated by the CEC in a blinded manner. All events are also sub-categorized into fatal and non-fatal. For all endpoints blindly adjudicated by the CEC, the CEC's interpretation prevails and is used in the statistical analyses.
Planned Sample Size: The plan is to enroll 1500 subjects (750 per arm).	Based on a review of available safety data, the estimated one-year event rate of the primary endpoint (MCRB, i.e. ISTH major or clinically relevant non-major bleeding) under the VKA-based antithrombotic regimen is 24%. The edoxaban-based antithrombotic regimen is anticipated to reduce the one-year incidence to 18% (a relative risk (RR) of 0.75). Under the assumption of an exponential distribution, the hazard ratio equals 0.7231. The accrual of2 x 712 evaluable subjects provides 80% power to demonstrate superiority of the edoxaban-based antithrombotic regimen over the VKA-based antithrombotic

regimen at a two-sided a=0.05. To compensate for censoring, the final sample size is set at 2 x 750 subjects.

Statistical Analyses: Four analysis sets are defined:

- The *Intention-to-treat (ITT) analysis set* consists of all randomized subjects irrespective whether they received a single dose of the randomized study regimen 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:
  - A major violation of the inclusion criteria
  - An unequivocal violation of the exclusion criteria, (for more details, see Section 11.1.3)
- The *Safety (SAF) analysis set* 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 (date and time of randomization or date and time of first study edoxabari or study VKA intake) to Day 365.

'OverallStudy Period+ 30 days': This period is defined as the time from the reference data (date and time of randomization or date and time of first study edoxaban or study VKA intake) to Day 395.

'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 of final dose of study edoxaban or study VKA plus 30 days, including study regimen interruptions.

The main analysis of all adjudicated primary and secondary exploratory endpoints will be based on ITT analysis set and taking the first adjudicated event during the 'overall study period' into account.

For each of the primary and secondary exploratory endpoints, appropriate summary statistics (e.g. event rate) including 95% 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 randomizatio,n- (IXRS) as covariates, to provide point estimates and 95% Confidence Interval (Cl) 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 detem1ined an individual basis for subjects with incomplete follow-up.

For time to first event analyses based on the ' overall study period', cumulative event rates over time are summarized using the Kaplan-Meier method.

There are two primary hypotheses for the primary endpoint to be tested in this study.

- The edoxaban-based antithrombotic regimen is non-inferior to the VKA-based antithrombotic regimen with regards to MCRB.
- The edoxaban-based antithrombotic regimen is superior to the VKA-based antithrombotic regimen with regards to MCRB.

These two hypotheses are tested in a hierarchical manner, non-inferiority followed by superiority to control the type-I error rate, with adequate power for each of the two hypotheses.

The *primary analysis to show non-inferiority* wm'be based on first occurrence of an (adjudicated) MCRB that occurred during the 'overall study period' for all subjects belonging to the ITT analysis set and applying the aforementioned statistical method. The edoxaban-based regimen will be considered non-inferior to the VKA-based regimen, if the upper boundary of the two-:sided 95% CI for HR falls below 1.20.

The *primary analysis to show superiority* will be based on first occurrence of an (adjudicated) MCRB that occurred during the 'overall study period' for all subjects belonging to the ITT analysis set and applying the aforementioned statistical method. The edoxaban-based regimen will be compared with the VKA-based regimen for superiority only if the non-inferiority of the

edoxaban based regimen is established first. The edoxaban-based regimen will be considered superior to the VKA-based regimen, if the upper boundary of the two-sided 95% CI for HR falls below 1.00.

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', 'overall study period+ 30 days' will be presented but should be interpreted in a more descriptive way.

The *main analysis for all secondary exploratory 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.

All details of the statistical analysis will be described in a statistical analysis plan (SAP).

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACS	Acute Coronary Syndrome
AE	Adverse Event
AESf	Advei·se Event of Special Interest
AF	Atrial Fibrillation
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ARC	Academic Research Consorti um
ARO	Academic Resea, h Organization
AST	Aspartate Transaminase
ASA	Acetylsalicylic Acid
BARC	Bleeding Academic Research Consortium
BP	Bloo d Pressure
BUN	Blood Urea Nitr gen
CAD	Coronary Artery Disease
CABG	Coronaty Atiery Bypass Graft
CrCL	Creatinine Clearance
CEC	Clinical Events Committee
CKD-EPI	Chronic Kidney Disease Epidemiology
CKMB	Creatine Kinase MB Isoform
CRNM	Clinically R levant Non-Major
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
cTn	Cardiac Troponin
CV	Cardiovascular
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medical Agency
EOT	End-of-Treatment
EIU	Exposure In Utero
EudraCT	European Union Drug Regulati ng Authorities Clinical Trials
FXa	Factor Xa
GCP	Good Clinical Practice (refers to ICH)
GI	Gastrointestinal
Hct	Hematocrit
Hgb	Hemoglobin
HR	Hazard Ratio
1B	Investigator Brochure

ABBREVIATION	DEFINITION
IC	Informed Consent
!CF	Informed Consent Form
ICH	Interi1ational Conference on Harmonization
1D	Identiftcation
IEC	Independent Ethics Committee
-INR	International-Norma lized-Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
ITT	Intent-To-Treat
IXRS	Interactive Web/Voice Response System
LLT	Lower Level Term
MCRB	Major or Clinically Relevant Non-major Bleeding
MEE	Main Efficacy Endpoint
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
mITT	Modified ITT
NCB	Net Clinical Benefit
NOAC	Non-vitamin K Antagonist Oral Anticoagulant
NSAID	Non-Steroidal Anti-Inflammatory Drug
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulant
P-gp	P-Glycoprotein
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamic
PK	Pharmacokinetic
pp	Per Protocol
PROBE design	Prospective, Randomized, Open-label study with Blinded Evaluation of endpoints
pSOC	Primary System Organ Class
SAE	Serious Adverse Event
SAF	Safety.
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SEE	Systemic Embolic Events
SAVER	Serious Adverse Event Report
SOP	Standard Operating Procedures
SmPC	Summary of Product Characteristics
SUSAR	Suspected, Unexpected, Serious Adverse Reaction
TBL	Total Bilirubin
TIA	Transient Ischemic Attack
ULN	Upper Limit of Normal
VKA	Vitamin K Antagonist

ABBREVIATION	DEFINITION
Vs	Versus
VTE	Venous Thromboembolic Event
WBC	White Blood Cells

1. INTRODUCTION AND BACKGROUND INFORMATION

Up to one-third of patients with atrial fibrillation (AF) have concomitant coronary artery disease (CAD) and may require stent placement to treat symptomatic stable CAD or acute coronary syndromes (ACS).(2) The optimal antithrombotic treatment for patients with AF following coronary stenting has not be n well established. (1, 3)

Dual antiplatelet therapy with aspirin and P2Y12 antagonist is cmTently recommended after PCI with stent placement.(4, 5)

Chronic oral anticoagulation is recommended in patients with AF at moderate or high risk of thromboembolism.(6, 7) Non-vitamin K antagonist oral anticoagulants (NOACs) are an alternative to Vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular AF (NVAF). (3)

Therapy with an oral anticoagulant (OAC), aspirin, and clopidogrel (P2Y12 inhibitor) is generally considered the standard of care for patien-ts with AF following coronary stent placement.(1, 3, 4) Consensus recommendations (1, 8-10) have endorsed the use of such therapy with the duration of treatment with the individual drngs being guided by type of stent, bleeding risk, and clinical presentation (i.e., stable coronary disease or acute coronary syndrome (ACS]).(1, 7-11) However, therapy with OAC, aspirin and clopidogrel is associated with 3- to 4-fold increased risk of bleeding complications.

The 2014 AHA/ACC/HRS AF guidelines (11) state that "following coronary revascularization (percutaneous or surgical) in patients with AF.and a CHA2DS2-VASc score of2 or greater, it may be reasonable to use clopidogrel (75 mg once-daily) concurrently with O C but without aspirin." This recommendation is class Ilb, such that it "may/might be considered," "usefulness/effectiveness is unknown/unclear/uncertainor not well established," and "additional studies with broad objectives needed." The "level of evidence B" is based on the WOEST trial (12), a relatively small exploratory study in which therapy with V,{(A plus clopidogr l was associated with a significant reduction in bleeding complications and fewer thrombotic events compared with therapy with VKA, aspirin, and clopidogrel.

Edoxaban is a factor X;:i inhibitor (NOAC); tested in the ENGAGE AF-TIMi 48 trial.(13) Edoxaban was non-inferior to warfarin (VKA) with respect to the prevention of stroke or systemic embolism and was associated with significantly lower rates of bleeding and death from cardiovascular causes in patients with non-valvular AF.(13)

There are insufficieI_lt data on the safety and efficacy of edoxaban plus antiplatelet therapy in subjects with AF following PCI with stenting. This study is designed to evaluate the safety and to explore the efficacy of an edoxaban-based antithrombotic regimen versus a VKA-based antithrombotic regimen in subjects with AF following PCI with stent placement. Bleeding is a central safety outcome in cardiovascular clinical trials, especially for antithrombotic strategies and invasive procedures (14-16).

1.1. Data-Summary

1.1.1. Investigational Product

1.1.1.1. Name

Name oflnvestigational Product: Edoxaban tosylate (DU-l 76b).

Edoxaban (InternationaJ-non-::proprietary - na me)-;-an hydrousfree-base-(DU-176).

1.1.1.2. Description

Edoxaban tosylate is an antithrombotic agent, an or lly active, selective, direct, and reversible inhibitor of Factor Xa (FXa), manufactured by Daiichi Sankyo Co., Ltd., Japan. Inhibition of FXa in the coagulation cascade prolongs clotting time and potentially reduces the risk of spontaneous or induced thrombus formation.

Edoxaban refers to the anhydrous free base of edoxaban tosylate. Subjects are given edoxaban tosylate (a monohydrate salt) but all doses and plasma concentrations are expressed in terms of edoxaban, the anhydrous free base.

For simplicity, this protocol uses the term "edoxaban" to refer to either or both forms.

1.1.1.3. Intended Use Under Investigation

The proposed indication is to use edoxaban in subjects with AF following successful PCI with stent placement.

1.1.1.4. Nonclinical Studies

In nonclinical studies, edoxaban showed excellent potential as an antithrombotic agent. Results of non-clinical toxicology studies do not indicate ariy major clinically concerning adverse effects in study animals exposed to edoxaban. Additional details are available in the edoxaban Investigators' Brochure (17).

1.1.1.5. Clinical Experience

Edoxaban has been approved and is marketed in Japan for the indication of prevention of ischemic stroke and systemic embolism in patients with non-valvular AF; treatment and recurrence prevention of venous thromboembolism (VTE) (deep vein thrombosis and pulmonary thromboembolism); and prevention ofvenous thromboembolism in patients undergoing any of the following rthopedic procedures on the lower limb: total knee replacement, total hip replacement, and hip fracture surgery.

The efficacy and safety of edoxaban for reducing the risk of stroke and SEE in subjects with non-valvular AF has been demonstrated in a large pivotal Phase 3 study (ENGAGE AF-TIMI 48) (13).

Similarly, the efficacy and safety of edoxaban for the treatment of VTE, including deep vein thrombosis and pulmonary embolism, and the prevention of recurrent VTE has been demonstrated in a Phase 3-Hokusai VTE study(18).

Features of the Hokusai VTE and ENGAGE AF-TIMI 48 studies are summarized in Table 1.1.

Table 1.1: Summary of the Hokusai VTE and ENGAGE AF-TIMI 48 Studies

Study Population	Median Duration of Treatment	Treatment Groups	N	Primary Efficacy Outcome		Primary Safety Outcome	
				Endpoint	HR (95% CI) Edoxaban vs Warfarin	Endpoint	HR (95% CI) Edoxaban vs Warfarin
Hokusai VTE (acute VTE)	0.7 years	Edoxaban_60 mg	,U !8	"Recur rent VTE	0.89 (0.103,-1.128)_ mIIT , overall study period	Major-+- CRNM _ Bleeding	0.8 1-(0.705 , 0.936) mIIT , on-treatment period
		Warfarin	4122				
ENGAGE AF-TIMI 48 (NVAF)	2.5 years	Edoxaban High Dose Regimen*	7035	Stroke and SEE	0.79 (0.63, 0.99) mITT, on-treatment period	Major Bleeding	0.80 (0.71, 0.91) mITT, on-treatment period
		Edoxaban Low Dose Regimen**	7034		1.07 (0.87, 1.3I) mIIT, on-treatment period		0.47 (0.41, 0.55) m!IT on-treatment period
		Warfarin	7036		.		-

Abbreviations: CI = confidence interval; CRNM = clinically relevant non-major; HR = Hazard Ratio; NVAF = nonvalvular atrial fibrillation; SEE= systemic embolic event; vs= versus; VTE = venous thromboembolism; mlTT = modified intention-to-treat; N = number of subjects
*High Dose Regimen= 60mg edoxaban once-daily with reduction to 30mg once-dafly in patients with low body weight, moderate renal impairment, or specified concomitant medications;
**Low Dose Regimen= 30mg edoxaban once-daily with reduction to I5mgonce-daily in patients with low body weight, moderate renal impairment, or specified concomitant medications.

Other completed studies include Phase I clinical pharmacology studies, Phase 2 dose-ranging studies in subjects with NYAF'and subjects undergoing lower-extremity orthqpedic surgery, and Phase 3 studies in subjects undergoing lower-extremity orthopedic surgery.

In the course of the edoxaban clinical development program, oyer 23,500 subjects have been given edoxaban encompassing over 34,100 subject-years of exposure.

The safety and efficacy *bf* edoxaban has been evaluated in the following programs:

- Phase I studies (including 1627 subjects from pharmacokinetic (PK)-pharmacodynamic (PD) studies, PK in subjects with renal impairment, and drug-drug interaction studies): Results of these studies have shown that edoxaban is rapidly absorbed with rapid onset of action and the dose concentration relationship is generally linear. The mean terminal half-life ranges between 5 and 11 hours. The pharmacodynamic effect as measured by anti-Xa activity or inhibition of factor Xa activity lasts for 24 hours. Dose-related increases in PK concentrations and anti-thrombotic activity were observed, as measured by anti-Xa activity. The bioavailability is ~60% and 50% of the absorbed drug is excreted by renal clearance. The absorption, distribution, metabolism, and excretion are also mediated through the P glycoprotein (P-gp) transport system and drugs with P-gp inhibitory effects may alter edoxaban exposure.
- Phase 2 studies in AF subjects (including 1,952 subjects): These studies primarily evaluated safety of different dose regimens of edoxaban with approximately 12 weeks of treatment. Results of these studies showed that the twice a day (BID) regimen had higher

bleeding than once-daily regimen of edoxaban. Consequently, the once-daily regimen of edoxaban was tested in the subsequent Phase 3 trials.

- Phase 3 pivotal trial (ENGAGE AF-TIMI 48(13)) involving 21,105 subjects with a median follow-up of 2.8 years. Two once-daily regimens of edoxaban were compared with warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Both regimens were non-inferior to warfarin for the prevention of stroke and systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. Edoxaban has been approved for marketing in US and in Europe for this indication.
- Phase 2/3 VTE prophylaxis studies in subjects undergoing orthopedic surgery (including 3,678 subjects). Edoxaban has been approved for marketing in Japan for this indication.
- Phase 3 pivotal trial (Hokusai-VTB (18)) involving 8,292 randomized subjects. Edoxaban administered once-daily after initial treatment with heparin was non-inferior to standard therapy and caused significantly less bleeding in patients with VTE.

1.2. Study Rationale

Up to one-third of patients with AF have concomitant coronary artery disease and may require stent placement to treat symptomatic stable coronary artery disease or acute coronary syndromes. The optimal antithrombotic treatment for patients with AF following coronary stenting has not been well established.

This study is designed to evaluate the safety and to explore the efficacy of an edoxaban-based antithrombotic regimen versus a VKA-based antithrombotic regimen in subjects with AF following PCI with stent placement.

1.2.1.1. Dose rationale

Based on the results of the ENGAGE AF-TIMI 48(13) and Hokusai(18) 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 PCI with stent placement but no additional evidence exists suggesting further dose adaptation.

1.3. Risks and Benefits for Study Subjects

Subjects with AF undergoing PCI with stent placement require the use of OACs with single or dual antiplatelet therapy (i.e., a $P2Y_{12}$ antagonist and acetylsalicylic acid such as aspirin) to reduce the risk of stroke, SEE, stent thrombosis and other myocardial ischemic events, and related cardiovascular morbidity and mortality. While the concomitant use of OACs with antiplatelet agents reduces the risk of thromboembolic events, such therapy also increases the risk of bleeding events. 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(19).

1.4. 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 International Council for Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s):

- European Commission Directive (2001/20/EC Apr 2001);
- European Commission Directive (2005/28/EC Apr 2005);
- European Data Protection Directive 95/46/EC;
- Other applicable local regulations.

1.4.1. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in ccordance with GCP, the rules laid down for the protection of individuals with regard to the processing of personal data and the free movement of such data and other 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 regard 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 Case Report Forms (CRFs) or other documents submitted to the Sponsor, subjects should be identified by a unique subject identification number as designated by the sponsor. The Investigator must obliterate any private information contained on documents (e.g. name or address) prior to passing them oil to the sponsor or CRO. Documents that are not for submission to either Sponsor or CRO (e.g., signed Informed Consent [IC]) 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 Independent Ethics Committee (IEC) direct access to review the subject's original medical records for _verification of study-related procedures and data.

1.4.2. Informed Consent (IC) Procedure

Before a subject's participation in the study, it is the Investigator's responsibiJity 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 screening procedures or any study drugs are administered. Subjects must have the opportunity to ask questions and receive satisfactory answers to their inquiries, and must have adequate time to decide whether or not to participate in the study. The written ipformed consent form (ICF) is prepared in the local language(s) of the potential subject population.

1.4.3. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator's Brochure, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures, information about payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the IEC 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 arid/or the Statistical Analysis Plan (SAP).

All subsequent substantial protocol amendments and changes to the IC document will be submitted to the IEC for approval. The Investigator should notify the IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or delegate will insure all legal aspects are covered, and approval of 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 the appropriate notification of or approval by the relevant regulatory bodies.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective is to compare a 12-month antithrombotic regimen of edoxaban in combination with clopidogrel or another P2Y12 antagonist against a regimen of a VKA in combination with clopidogrel or another P2Y12 antagonist and at least 1-month ASA in subjects with AF following successful PCI with stent placement in terms of the incidence of major or clinically relevant non-major ISTH-defined bleeding (MCRB).

There are two primary hypotheses for bleeding to be tested in this study.

- The edoxaban-based antithrombotic regimen is non-inferior to the VKA-based antithrombotic regimen with regards to MCRB.
- The edoxaban-based antithrombotic regimen is superior to the VKA-based antithrombotic regimen with regards to MCRB.

These two hypotheses are tested in a hierarchical manner, non-inferiority followed by superiority to control the type-I error rate, with adequate power for each of the two hypotheses.

2.1.2. Secondary Exploratory Objectives

Secondary exploratory objectives of the study are to compare the edoxaban-based antithrombotic regimen to the VKA-based antithrombotic regimen with regard to:

- Main efficacy endpoint (MEE), defined as the composite of cardiovascular (CV) death, stroke, systemic embolic events (SEE), myocardial infarction (MI) and definite stent thrombosis.
- Net clinical benefit (NCB), defined as the composite of CV death, stroke, SEE, MI, definite stent thrombosis and ISTH-defined major bleeding.
- Main thromboembolic event, defined as composite of cardiac or thromboembolic death (thromboembolic death considered to be thromboembolic in origin (including thromboembolic stroke, pulmonary embolism, any other systemic embolism), ischemic stroke, SEE, MI and definite stent thrombosis.
- ISTH-defined major bleeding
- Any bleeding defined as the composite of major, clinically relevant non-major, and minor bleeding (ISTH definition)
- Symptomatic intracranial hemorrhage (ICH)
- Composite of stroke and SEE
- Composite of all-cause death, stroke, SEE, MI and definite stent thrombosis
- Composite of CV death, MI and definite stent thrombosis

- The single components of the composite primary and secondary endpoints mentioned above are explored
- Safety parameters such as (serious) adverse events, laboratory parameters, ECG and vital signs.

2-:-1:J. **Otfier Ooject1ves**

Not applicable.

3. STUDY DESIGN

3.1. Overall Plan

This is a multinational, multicenter, randomized, open-label Phase 3b study with blinded evaluation of endpoints by an independent CEC (PROBE design). At least 150 sites will be required to enroll 1500 subjects (750 subjects per antithrombotic regimen) in Europe, and Asia-Pacific

A schematic presentation of the study design is provided in Figure 3.1.

The study is divided into a screening period (incl. pre-screening), a treatment period and an observational post-treatment follow-up period. The screening period starts after a percutaneous coronary intervention (PCI) with stent placement. Subjects with an OAC indication for AF for at least 12 months who have successfully undergone a PCI and who received a stent are eligible for inclusion in the study.

Subjects should satisfy the pre-screening criteria before IC is signed. Once written, IC is obtained, and eligibility criteria (inclusion and exclusion) are met subjects are randomized without delay (1:1 ratio), to one of two treatment groups being an edoxaban-based regimen (index regimen) and a VKA-based regimen (control regimen). Consenting and randomization takes place within 4 hours and 5 days post-PCI and before hospital discharge. If a staged PCI is planned, consenting and randomization takes place after successful completion of the last stage.

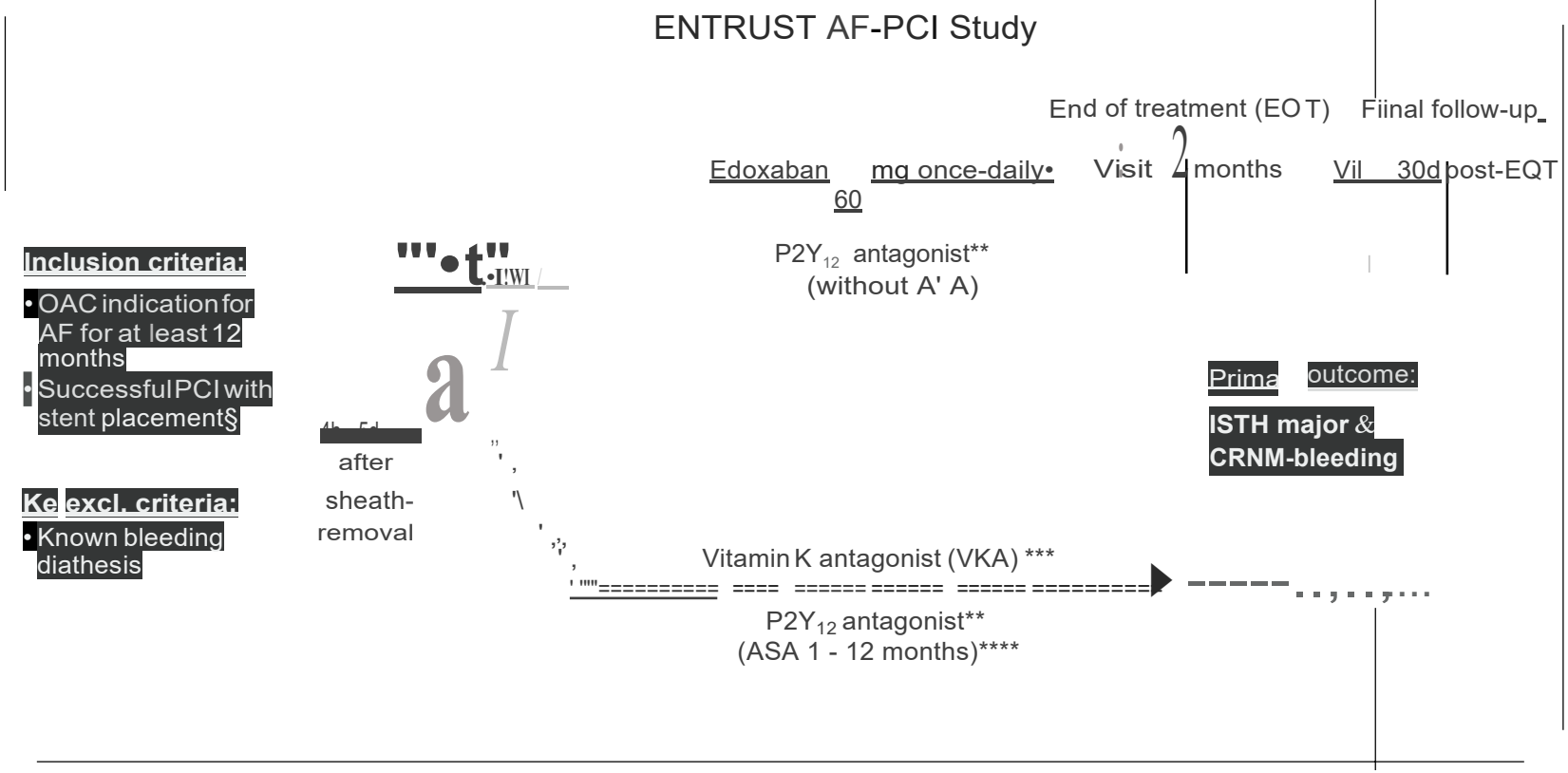
The edoxaban-based regimen consists of treatment with edoxaban 60 mg once-daily and clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 or 10 mg once-daily] /or ticagrelor [90 mg twice-daily]) for 12 months.

The VKA-based regimen, dosed to achieve a target INR of 2.0- 3.0, in combination with clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 or 10 mg once-daily] /or ticagrelor (90 mg twice-daily]) for 12 months and ASA (100 mg once-daily) for 1-12 months. These regimens are detailed in Section 5. The assigned regimen is implemented after randomization without any due delay (please refer to Section 5). The randomized regimens (edoxaban-based or VKA-based) and clopidogrel (or other P2Y12 antagonist) are continued for 12 months, when the scheduled end-of-treatment (EOT) is reached.

Subject clinical visits are planned at 1, 3, 6, 9 and 12 months after randomization. All subjects have telephone assessments at 2, 4, 5, 7, 8, 10 and 11 months after randomization. All information must be captured in the eCRF and study assessments are performed according to the visit schedule provided under appendix Section 17.9. All subjects are followed for 12 months irrespective of changes in the antithrombotic regimen. Clinical follow-up is only terminated at the explicit request of the subject. All subjects on either edoxaban or VKA at 12 months, have a contact planned 1 month after the end-of-treatment visit, to collect data on targeted concomitant medications, SAEs, and other events of interest. The overall duration of subject participation from screning through follow-up is therefore approx. 13 months.

The study organization, including the CEC, DSMB, Executive Committee and Steering Committee are described in appendix section 17.1. An independent DSMB reviews pertinent study data to protect the safety of the subjects participating in the study.

Figure 3.1 Study Design



• Edoxaban dose reduction to 30 mg once-daily if either CrCL s 50 mUmin, or body weight s 60 kg, or concomitant therapy with certain P-gp inhibitors. •• Clopidogrel 75mg once-daily (or in the presence of a documented clinical need prasugrel [5 or 10 mg once daily] / ticagrelor [90 mg twice daily] may be used).••• VKA of choice with dosing for target international normalized ratio (INR) of.2 0 - 3.0 inclusive .....ASA (100 mg once-daily) for 1-12 months guided by the clinical presentation (ACS or stable coronary isease), and upon the CHA_2DS VASc and HAS-BLED score.

§ Goal of at least 25% ACS.

AF, atrial fibrillation: ACS, acute coronary syndrome: PCI, percutaneous coronary intervention; ISTH, International Society on Thrombosis and Haemostasis; CRNM, clinically relevant non-major; h, hours: d, days.

4. STUDY POPULATION

4.1. Enrollment

Investigators maintain a confidential pre-screening log of all potential study candidates (i.e. subjects with an OAC indication for AF for at least 12 months who have successfully undergone a PCI) that includes limited information of the subjects (age, sex), date and outcome of screening process (e.g:, enroll in the study, reason for refusal to participate).

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 list. 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.

A subject is considered to be enrolled after the subject has provided written IC. An unique study identification number is provided through the IXRS together with the randomized treatment assignment.

4.1.1. Inclusion Criteria

OAC indication for atrial fibrillation for a period of at least 12 months following successful PCI with stenting in adult male and female patients 2:18 years of age.

Eligibility is assessed 4 hours after sheath removal and within 5 days after successful PCI with stent placement. If a staged PCI is planned, eligibility is assessed after completion of the last stage.

Successful PCI definition:

The success of a PCI procedure is defined by 2 interrelated components: angiographic findings, procedural / clinical outcomes as detailed below:

a) Angiographic Success

A minimum stenosis diameter of< 20% (as visually assessed by angiography - residual blockage or stenosis reduced to less than 20% of the artery's diameter).

Sufficient enlargement of the lumen at the target site to improve coronary artery blood flow with final TIMI flow grade 3 (visually assessed by angiography), without occlusion of a significant side branch, flow-limiting dissection, distal embolization, or angiographic thrombus.

b) Procedural Success

No major in-hospital clinical complications (e.g. ongoing ISTH qiajor or clinical relevant non-major procedural bleeding at the time of randomization, stroke, emergency CABG).

In summary, a **clinically successful PCI** requires both anatomic and procedural success along with relief of signs and/or symptoms of myocardial ischemia at the time of randomization.

4.1.2. · Exclusion Criteria

Subjects who meet any of the following critena are disqualified from entering the study:

Bleeding risks or systemic conditions

1. Known bleeding diathesis, including but not limited to,
    a. Uncontrolled active bleeding, encompassing both ISTH major and clinically relevant non-major bleeding, preceding randomization.
    b. Lesion or condition, if considered to be a significant risk for major bleeding.

This may include but is not limited to: unresolved gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding (e.g. malignancies with metastasis), recent unresolved brain or spinal injury, recent brain; spinal or ophthalmic surgery, any intracranial hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms (of more than 3.5 cm) or major intraspinal or intracerebral vascular abnormalities.

Medication-related

2. INR > 2.5 (the subject can be reconsidered at a later time, but within 5 days· of sheath removal).
3. Contraindication to edoxaban, VKA, ASA and/or P2Y12 antagonists;
4. Concomitant treatment with other antithrombotic agents, fibrinolytic therapy n4 chronic nonsteroidal anti-inflammatory drugs (NSAIDs).

Concomitant copditions and therapies

5. Critically ill or hemodynamically unstable subjects (at the time of randomization) including:
    a. cardiogenic shock or acute decompensated heart failure, with the requirement for vasopressor agents or inotropic support or mechanical support to support circulation
    b. respiratory failure requiring endotracheal intubation and mechanical ventilation.
6. Ariy prior mechanical valvular prosthesis;
7. Planned coronary or vascular intervention or major surgery within 12 months; Randomization must be deferred to the last stage in a multistep, multivessel PCI procedure;
8. Moderate or severe mitral stenosis;
9. Ischemic stroke within 2 weeks prior to randomization;

10. Uncontrolled severe hypertension with a systolic blood pressure (BP) 2.180 mmHg and/or diastolic BP 2. 120 mmHg;
11. End stage renal disease (ESRD) (CrCL < 15 mL/min) or on dialysis;
12. Known abnormal liver function prior to randomization (incl. hepatic disease or biochemical evidence of significant liver derangement known prior to randomization) (see appendix 17.4).

Other exclusion criteria

13. Any of the following abnormal local laboratory results prior to randomization:
    a. Platelet count < 50 x10^9/L
    b. Hemoglobin < 8 g/dL.
14. Unable to provide written TC;
15. Female subjects of childbearing potential without using highly effective contraception (female of childbearing potential is defined as one who has not been postmenopausal for at least one year, or has not been surgically sterilised, or has not had a hysterectomy at least three months prior to the start of this study). Females taking oral contraceptives should have been on therapy for at least three months. Adequate contraceptives include: Combined (estrogen and progestogen containing) oral, intravaginal or transdermal hormonal contraception associated with inhibition of ovulation;. progestogen-onlyoral, injectable or implantable hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence
16. Pregnant or breast-feeding subjects;
17. Assessment that the subject is not likely to comply with the study procedures or have complete follow-up;
18. Participating in another clinical trial that potentially interferes with the current study;
19. Previous randomization in this study;
20. Active on prescription drug abuse and addiction; abuse of illicit substances (i.e. marijuana; cocaine, methamphetamine heroin) and alcohol abuses during the last 12 months according to the judgement of the investigator
21. Life expectancy < 12 months.

4.2. Screening failures

Subjects are pre-screened based on the information available from the standard care. For subjects fulfilling the pre-screening (i.e., OAC indication for AF for a period of at least 12 months and successful PCI with stenting), IC signature and other study-specific screening procedures take place just prior to randomization. A

subject who withdraws IC before randomization or who fails the inclusion/exclusion criteria before randomization is defined as a screening failure. No further clinical follow-up is performed for these subjects.

4.3. Removal of Subjects From Therapy

4.3.1. Reasons for Withdrawal/Early Discontinuation

The subject is free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it. It is also possible that the sponsor or the competent authorities request termination of the study if there are concerns about conduct or safety.

Participation of a subject in this clinical study should be discontinued at all periods (except where noted) for any of the following reasons:

1. Withdrawal of Subjects consent at any time of the study
2. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk (including inter alia, stent thrombosis and major haemorrhage) and/or does not allow the subject to adhere to the requirements of the protocol.
3. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, other medical condition, or change in the subject's condition which indicates to the Investigator that continued participation is not in the best interest of the subject for any reason, including ethics.
4. Females who become pregnant at any time during the study period must be discontinued immediately and counselled appropriately. The Investigator must follow the pregnancy to completion of term.
5. Requirement of prohibited concomitant medication.
6. Subject failure to comply with protpcol requirements or study related procedures.
7. Termination of the study by the Sponsor or regulatory authorities.
8. When patients reach a primary endpoint or key safety endpoint (including but not limited to definite acute stent thrombosis, disabling stroke (modified Rankin score 2 at 90 days plus increase in 1 mRS category from the pre-stroke baseline)), the investigator needs to decide if study medication will be permanently discontinued, interrupted, modified or continued. In case of intracranial bleeding the protocol mandates stopping the study treatment.

If a subject withdraws from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last study medication dose and the reason for withdrawal.

If the subject is withdrawn due to an AE (including clinically relevant laboratory abnormalities); the Investigator will follow the subject until the AE has resolved, stabilised, or can be explained by reasons not attributable to the investigational product.

All subjects who are withdrawn from the study should complete protocol specified withdrawal procedures (Section 6.2.3 end of study).

4.3.2. Withdrawal procedures

If the Investigator removes a subject from the study or if the subject withdraws consent for any reason after receiving the first dose, a complete set of Early Withdrawal visit should be carried out, preferably prior to the subject being placed on alternative therapy.

An Early Withdrawal Visit will include the same assessments and procedures as the end-of-treatment visit (section 6.2.3). Additionally, the date study medication was last taken will be recorded. The Investigator should start the subject on appropriate oral anticoagulant treatment (see section 5.3.) and the prescription should be recorded in the eCRF, if the information is available.

All results of evaluations and observations, pertinent to the study, together with a description ofreason(s) for withdrawal must be recorded in the eCRF. If a subject is withdrawn from the study due to an AE, the event must be recorded on the AE page of the eCRF. Any additional study-specific procedures conducted due to the AE should be recorded on the eCRF as an unscheduled procedure. Any subject with an SAE or an AE that led to study medication discontinuation will be followed until the subject returns to baseline conditions or stabilises.

4.3.3. Study or ite terminations

If the Sponsor or their representatives, Investigator, or CA officials discover conditions during the study that indicate that the study or site involvement should be terminated. Conditions that may warrant termination of the study or involvement of a study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enroll.ed in the study.
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluatiqn, or development of the study drug.
- Failure of the Investigator(s) to comply with pertinent clinical trial regulations.
- Submission of knowingly false information from the research facility to the Sponsor, Clinical Monitor, or the Clinical Research Assistant.
- Insufficient adherence to protocol requirements
- Study termination and follow-up will be performed in accordance with applicable local regulations."

4.4 Subject Replacement

Not applicable.

4.5 Subject Re-screening Procedures

If during study qualification:

- a staged PCI is planned, eligibility is assessed after completion of the last stage of PCI

5. TREATMENT REGIMENS ADMINISTERED

5.i. Method of Assigning Subjects to-Treatment Regimens

After the IC has been signed and eligibility confirmed, the Investigator contacts the IXRS to assign an individual study identification number.

The Investigator should be prepared to provide subject information, including, but nor--limited-to:age ;-bodr weight, clinical presentation[ACS ot stable, coronary artery disease (CAD)], CrCL using Cockcroft-Gault formula (see Section 17.6) and whether the subject is taking concomitant P-gp inhibitors requiring edoxaban dose reduction (according to local SmPC or 1B as applicable).

Randomization is stratified by clinical presentation (ACS or stable coronary disease), requirement for dose adjustment of edoxaban, and by geographical region (i.e. Latin America, Western Europe, Eastern Europe, Asia, as applicable).

Subjects will be assigned randomly via the above mentioned IXRS such that the study has a I:1 ratio of subjects in the two antithrombotic treatment regimens.

The specifications for generation of the randomization schedule will be prepared by the study biostatistician and the IXRS vendor. An independent biostatistician, not otherwise part of the study team, will generate the randomization schedule. For this study, the randomization schedule refers to a list that includes the subject identification number (ID), randomization block' number, and randomization treatment.

5.2. Study Treatment Regimens

5.2.1. Edoxaban-based regimen for 12 months

- Edoxaban 60 mg once-daily or 30 mg once-daily in selected subjects (see Section 5.3.1).
- Clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used).
- The use of a P2Y12 antagonist other than clopidogrel must be pre-declared.
- Concomitant use bf another anti-platelet agent (i.e. ASA) is not allowed.

5.2.2. VKA-based regimen for 12 months (control regimen)

- Oral VKA of choice with dosing for target international normalized ratio (INR) between 2.0 - 3.0, inclusive.
- Clopidogrel 75mg once-daily (or in the presence of a documented clinical need prasugrel [10 mg once-daily]/ ticagrelor [90 mg twice-daily] may be used).
- ASA (100 mg once-daily) for a minimum of 1 month and up to 12 months duration at the Investigator discretion guided by the clinical presentation

(ACS or stable CAD), and upon the CHA2DS2-VASc and HAS-BLED score (1).

- The useof a $P2Y_{12}$ antagonist other than clopidogrel must be pre-declared, together with the intended duration of ASA treatment.

For simplicity, this protocol uses the term "edoxaban" to refer to edoxaban tosylate, "clopidogrel" to refer to clopidogrel bisulfate and the term "prasugrel" to refer to prasugrel hydrochloride.
Pre-declaration means that the Investigator specifies this information in the IXRS, prior to randomization and assignment to an antithrombotic regimen.

3. Edoxaban

Edoxaban tosylate (DU-176b, trade names Lixiana®, Savaysa®), referred throughout this protocol by the term "edoxaban" for simplicity, is part of the edoxaban-based regimen. Please refer to Section 5.9 Labeling and Packaging.

According to local SmPC or IB as applicable, subjects may take edoxaban with or without food, in the morning or evening, but at approximately the same time every day.

If a dose of edoxaban is missed, the dose must be taken as soon as possible as long as on the same day. The dose of edoxaban must not be doubled to make up for a missed dose.

5.3.1. Dose

Edoxaban 60 mg once-daily.

At randomization, the recommended dose of edoxaban is 30 mg once-daily in subjects with 1 or more of the following factors:

- Moderate or severe renal impairment (calculated CrCL 15 - 50 mL/min),
- Low body weight of 60 kg (132 lbs),
- Concurrent use of P-gp inhibitors (please refer to local SmPC or to IB, as applicable).

  In EU countries, according to SmPC concomitant use of edoxaban with cyclosporine, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once-daily. Concomitant use of edoxaban with *quinidine, verapamil, or amiodarone* does *not require* dose reduction.

All edoxaban dosage adjustments will be implemented through the IXRS. The IXRS will provide the appropriate drug supply kit number.

J::or low body weight (::S 60 kg) present at randomization, the edoxaban dose is reduced permanently and even if the subject gains weight, the edoxaban dose remains reduced.

The dose of edoxaban returns to the regular dosage regimen of 60 mg once-daily any time the subject no longer displays any of the other above mentioned factors.

After randomization and in subjects without dose reduction, if subject's:

body weight drops to ::S 60 kg and the body weight change is > 10% of the subject's baseline body weight, then the edoxaban dose is reduced (i.e., to 30 mg once-daily) *permanently.*

CrCL becomes 15 to 50 mL/min and the CrCL change is> 20% of the subject' s baseline CrCL, then the edoxaban dose is reduced.

Develops the need for concomitant treatment with certain P-gp inhibitors which require edoxaban dose adjustment, then the edoxaban dose is reduced (i.e., to 30 mg once-daily).

The dose of 15 mg edoxaban once-daily is not indicated as monotherapy and is solely provided as part of transition from edoxaban 30 mg at the end of study (see Section 5.3.3).

5.3.2. Transitioning to edoxaba,n 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 eCRF.

Table 5.2: Transitioning to edoxaban at randomization

Switching to edoxaban		
From	**To**	**Recommendation**
VKA	edoxaban	Discontinue the VKA and start edoxaban when INR is :S 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 infusio·n and start edoxaban 4 hours later.

5.3.3. Transition from edoxaban at EOT

For subjects randomized to the edoxaban.,.based reg imen that require switching from edoxaban to another anticoagulant at the scheduled EOT (or due a premature edoxaban discontinuation) th following algorithm should be used.

Table 5.3: 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 I5 - 50 mt/min), low body weight, or use with certain 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 switchi ng 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 between 2.0 and 3.0. It is recommended to take into account the maintenance dose of VKA if the patient 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, edoxaban should be discontinued. Most patients (85%) should be able to achieve an INR 2.0 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 between 2.0 and 3.0. It is recommended that during the first 14 days of concomitant therapy the INR is measured at least 3 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 <u>option:</u> Discontinue edoxaban and administer a parenteral anticoagulant and VKA at tn.e time of the next scheduled edoxaban dose. Once a stable INR of 2.0 is achieved, the parenteral anticoagulant should be discontinued and the VKA continued.
edoxaban	Other non-VKAOAC drugs	Discontinue edoxaban and start the non-VKA anticoagulant at the time of the next scheduled dose of edoxaban.

Switching from edoxaban		
From	**To**	**Recommendation**
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.

5.4. Vitamin K Antagonist (VKA)

An approved/marketed VKA will be supplied as the preferred VKA for each selected country participating in the study. All VKA dispensations must take place through the IXRS that will provide the appropriate drug supply kit number.

In addition, the Investigator monitors the INR and adjusts the VKA dose to maintain the target INR between 2.0-3.0 inclusive. It is the Investigators responsibility to collect monthly INR assessments and record these throughout the study.

5.4.1. Dose

A preferred vitamin K antagonist (VKA) is selected for each participating country which is provided as study medication:-

Warfarin

Loading dose from 2 to 5 mg once-daily for 2-4 days followed by a maintenance dose of 2 to 10 mg once-daily adjusted by INR values to maintain target INR between 2.0 -3.0 inclusive.

Phenprocoumon

Weekly dose calculation ofup to 9 mg on day **1,** 6 mg on d y 2 and maintenance doses between 1.5 to 6.0 mg once-daily thereafter, adjusted by INR values to maintain target INR between 2.0 -3.0 inclusive.

Fluindione

The initial daily dose of 20 mg is adjusted by INR values to maintain target INR between 2.0 -3.0 inclusive. In subjects at particular risk of bleeding (weight <50 kg, elderly, hepatic impairment), the initial dose is usually lower. No loading dose should be used.

The dose adjustment is performed in accordance to the package insert and usually by increments of 5 mg (1/4 tablet).

Acenocoumarol

The usual starting dose in a normal weight person is between 2 mg/day to 4 mg/day without administration of a loading dose, if the INR value before the start of treatment is within the normal range. Trel:ltment may also be initiated with a loading dose regimen, usually 6 mg on the first day followed by 4 mg on the

second day. The maintenance dose generally lies between 1 and 8 mg once-daily, aμjusted by INR values to maintain target INR between 2.0 -3.0 inclusive.

The dosing of the aforementioned VK.As must be individualized. The maintenance dose varies from subject to subject and its appropriateness must b checked individually on basis of INR values.

The Investigator or designee is responsible for dispensing the VKA antagonist and mus ensure tfiat drug supplieffoy Sponsor is used in accordance with the protocol and the VKA package insert.

5.4.2. Transitioning to Study VKA at Randomization

For subj cts randomized to VKA who require switching from another anticoagulant (another VKA, other non-VKA OAC drugs 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.

Tal:ile 5.4: 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 ofrandomization is: • :52.5, start study VKA • > 2.5, the Investigator or designee must recheck at a later time; start study VKA when the INR is :52.5: document the INR value and the date it was measured.
Other non-VKA OAC drugs • dabigatran • rivaroxaban. • apixaban	StudyVKA	Ascertain adequate anticoagulation until an INR 2'.2.0 is reached and then continue with study VKA only. Follow local label of country-selected VKA and label ofNOAC being stopped for further guidance.
Parenteral anticoagulants	Study VKA	For subjects not previously on VKA, bridging with parenteral anticoagu lation is permissible, but not recommended. For initiation ofVKA therapy and related bridging with parenteral anticoagulation, follow locally 'established guidelines and local approved label (prescribing information) from the VKA manufacturer.

5.4.3. INR Management

Every effmt should be made to optimize the VKA dosing and INR monitoring schedule to maintain INR values between 2.0-3.0 inclusive.

INR management is according to the standard of care and may be performed by the Investigator, the subject's primary care physician or other private physician, at

a specialized anticoagulation clinic or patient self-monitoring. Close attention to the INR management plan and frequent monitoring of INR values is strongly recommended to optimize the VKA treatment and maintain the subject's INR values between 2.0-3.0 inclusive. The Investigator will ensure the VKA is used according to the approved label (prescribing information).

Daily INR determinations upon initiation should be obtained until subject's INR is stable in the therapeutic range. It may take 4-14 days to attain the target - - therapeutic range of INR 2'.. 2.0.

Obtain subsequent INR determinations as per recommendations and guidelines provided in the local approved label from the respective VKA manufacturer.

5.4.4. Transition from VKA at EOT

Table 5.5: Transitioning to Study VKA at EOT

Switching from VKA		
From	**To**	**Recommendation**
Study VKA	**VKA**	When transitioning a subject to post-study **VKA,** eit he·r maintain the subject on the same maintenance dose or adjust the dose ofVKA to maintain an TNR 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.

S.S. Clopidogrel (or alternative P2Y12 antagonist)

The P2Y12 antagonist clopidogrel is part of both the edoxaban-based and the VKA-based regimen. Please refer to Section 5.9 Labeling and Packaging.

5.5.1. Dose

Clopidogrel bisulfate 75mg once-daily as provided by sponsor.

In the presence of a documented clinical need (e.g. known hypersensitivity to clopidogrel or its_excipients, known CYP2C19 poor metabolizer-clopidogrel non-responder, among others) the use of a P2Y12 antagonist other than clopidogrel is allowed but must be pre-declared prior to randomization.

Either prasugrel [5 or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used according to the regional clinical practice guidelines for the dose and administration of the respective P2Y12 antagonist. The Investigator should follow

the relevant SmPC and the applicable regional guidelines regarding dose and transition from or to another P2Y12 antagonist.

The 5 mg once-daily dose of prasugr l should be give n as maintenance dose in subjects with body weight< 60 kg. The use of prasugrel in subjects 75 years of age is generally not recommended but if treatment is deemed necessary, then a reduced maintenance dose of 5 mg once-daily should be prescribed in subjects in this age group. For additional details please consult the SmPC and the drug--package insert.

Both prasugrel 5 or 10 mg once-daily and ticagrelor 90 mg twice-daily will be provided by the sponsor and dispensed through the IXRS. The Investigator or designee is responsible for dispensing the $P2Y_{12}$ antagonist through the IXRS and must ensure that drug supplied by sponsor is used only in accordance with the protocol and to the drug package insert.

5.5.2. Transitioning to study $P2Y_{12}$ antagonist at randomization

For subjects randomized to either the edoxaban-based or the VKA-based regimen discontinue the P2Y12 antagonist being taken and start study clopidogrel (or . alternative study P2Y12 antagonist) at the time of the next dose. Capture the date and timing of first study dose in eCRF.

5.5.3. P2Y12 inhibitor non-bleeding related adverse drug effect

Subjects must follow the P2Y12 antagonist pre-declared prior to randomization for 12 months. In the presence of a documented P2Y12 antagonist drug specific side effect excluding bleeding, cross-over to another study P2Y12 inhibitor .is allowed.

A P2Y12 inhibitor of similar potency is recommended wherever possible and if the treating physician considers it safe and the clinical situation allows doing so.

E.g.: subject on ticagrelor as pre-declared prior to randomization develops dyspnea as drug-specific side effect - cross-over to another P2Y12 is a llowed and prasugrel is recommended.

5.6. ASA

ASA is only part of the VKA-based regimen. Please refer to Section 5.9 Labeling and Packaging.

5.6.1. Dose

ASA 100 mg once-daily as provided by sponsor.is administered in the VKA-based regimen for a minimumof 1 month and up to 12 months. In case the ASA dose before randomization was other than 100 mg once-daily, the dose has to be adjusted to 100 mg once-daily immediately after randomization. The duration of the ASA treatme nt in the VKA-based regimen is pre-declared by the Investigator prior to randomization guided by the clinical presentation (ACS or stable coronary disease), and upon the CHA2DS2-VASc and HAS-BLED score. The Investigator follows the applicable regional clinical guidelines (1).

The Investigator or designee is responsible for dispensing ASA through the IXRS and must ensure that drug supplied by sponsor is used only in accordance with the protocol and to the drug package insert.

ASA is prohibited in the edoxaban-based regimen throughout the 12 months of planned treatment.

5.6.2 Transitioning to study ASA at randomization

For subjects randomized to the VKA-based regimen only discontinue ASA as being taken and start study ASA at the time of the next dose. Capture the date and timing of first study dose in eCRF.

5.7. Interruptions and discontinuations of the assigned regimen

The intended duration of the two treatment regimens is 12 months (i.e., 365 days). Subjects stay on the assigned OAC-based regimen as much as possible.

Permanent 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, 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 overdiuresis 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 dosedecreased 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. If refusal of the subject is restricted to a single study drug, this drug is discontinued while the other drugs are continued unchanged.

All subjects are followed for 12 months irrespective of changes in the antithrombotic regimen. Clinical follow-up is only terminated at the explicit documented request of the subject (see Section 6.5).

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

5.8. Method of Assessing Regimen Compliance

The first dose of each of the randomized study medication regimen is administered under nursing supervision. Each subject receives a medication log at each visit where missed doses should be captured and Investigator captures information in theeCRF.

At each visit, the Investigator or designee assesses the subject's compliance with the a signed regimen by asking the subject about missed doses and visually inspecting the drug supply the subject brought to the visit. The Investigator or designee assesses the compliance of edoxaban, P2Y12 antagonist and ASA by tablet counts, and captures information in the eCRF. If zero tablets are returned while an overage is expected, the subject should be asked whether any were disposed/thrown away, rather than taken orally.

Moreover, the Investigator captures the exposure to edoxaban, VKA, P2Y12 antagonist and ASA in the eCRF:

The information provided by the subject on their medication log.

Information provided by subject during site visits or site telephone assessments concerning missed doses (date, drug and reason).

For VKA, the Investigator assesses the INR at local lab at each on site visit and uses the determined INR value in the assessment ofVKA exposure and target INR between 2.0-3.0. In addition, the Investigator will contact the subject by telephone each month (if no visit is scheduled) and record INR valu.es in between site visits. It is the Investigators responsibility to:

- monitor the INR and adjust the VKA dose to maintain the INR within target
- collect monthly INR assessments and record these throughout the study.

In case of a suspected study endpoint, an additional assessment for subject . compliance to the assigned regimen must be performed.

5.9. Labeling and Packaging

The Investigators/study coordinators must ensure that the appropriate fields on the label are completed, including unique subject identification (ID).

The Investigator provides the subjects with sufficient study medications to last unti"l the next scheduled dispensing visit.

For each study medication, a **reserve kit** is provided at the first study regimen dispensation. The subject is instructed to use each medication pack completely before staiting a new pack. The reserve kit of each medication should only be used in case the s bject is out of study medication before reaching his/her next scheduled visit. If the reserve kit is needed, it must be used completely before starting a new pack. In this case the last kit of the next dispensation is changed to "reserve kit".

5.9.1. Edoxaban

Edoxaban is supplied as 15, 30 or 60 mg tablets in monthly wallets with blisters and will be provided to all sites. Materials are supplied in their original primary packaging and labelled with a single panel multilingual booklet.

5.9.2. VKA

Materials are supplied in their original primary packaging and labelled with a single panel multilingual booklet. Sponsor provides an oral preferred VKA as pre-selected by country, being either:

Warfarin supplied as commercially available tablets of **1** mg, and 2.5 mg in monthly wallets with biisters.

Phenprocoumon supplied as commercially available tablets of 3 mg strength in monthly wallets with blisters.

Fluindione supplied as commercially available tablets of 20 mg strength in monthly wallets with blisters. Fluindione suppl·y is exclusive to France and will not be available in other participating countries. Fluindione is only labelled in French.

- Acenocoumarol supplied as commercially available tablets of 4 mg strength in monthly wallets with blisters.

5.9.3. P2Y12 antagonist

Sponsor provides the $P2Y_{12}$ antagonists which is packaged in monthly wallets with blisters. Materials are supplied in their original primary packaging and labelled with a single panel multilingual booklet.

Clopidogrel will be supplied as commercially available 75 mg film-coated tablets. In addition, prasugrel and ticagrelor will also be provided for subjects with a documented clinical need and as pre-declared at randomization. Prasugrel will be supplied as commercially available 5 mg film-coated tablets. Ticagrelor will be supplied as commercially available 90 mg film-coated tablets.

5.9.4. ASA

Sponsor provides ASA whichis supplied as commercially available 100 mg tablets packaged in monthly wallets with blisters (primary package). Secondary protocol-specific packaging and labeling will be completed by an approved packaging and labeling facility according to GMP and national requirements.

5.9.5. Preparation

All investigational products will be supplied as tablets that need no further preparation at the sites.

5.9.6. Shipment receipt & Storage

When a drug shipment is received, the Investigator or designee will do the following within 48 hours of receipt: check the amount and condition of the drug, check for appropriate local language on the label, check the drug expiration date, and sign the Receipt of Shipment Form provided. The site will acknowledge receipt of the shipment in the IXRS. All instructions on the Receipt of Shipment Form will be followed, and the form will be filled in at the site. In addition, the Investigator or designee will contact the site monitor as soon as possible but within 48 hours, if there is a problem with the shipment.

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions as measured by a minimum/maximum thermometer. Temperature measurement will be recorded daily on a temperature log, excluding weekends and holidays. The sponsor and site monitor must be contacted in the event of a temperature excursion outside of the recommended storage conditions.

5.9.7. Drug Accountability

The eCRF contains a drug accountability module for any medications supplied by the sponsor. The Investigator or designee enters the required information in this module.

At the end of the study, or as directed, all medications supplied by the sponsor, including unused, partially used, or empty containers, will be returned to a designee as instructed by DSE. Investigational Product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of all study medications must be documented and the documentation included in the shipment. At the erid of the study, a final study medication reconciliation statement must be completed by the Investigator or designee and provided to the sponsor. Unused drug supplies may be destroyed by the Investigator when approved in writing by DSE and DSE has received copies of the site's drug handling and disposition SOPs.

All inventory forms must be made available for audits by a sponsor authorized representative or designee and /or inspections by regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused medications provided by the sponsor at the site.

5.9.8. Retention Samples

It is not be necessary to store retention samples of drugs at the study sites.

5.10. Prior and concomitant medications

Prior medications that the subject has taken within 30 days before randomization are recorded in the eCRF. These medications taken by the subjects prior to ranaomization or at any time during the studyare regarded as concomita medications and must be documented on the appropriate pages of the eCRF.

If the subject experiences a study endpoint event (see Section 7.land 7.2, including individual components) or an SAE, then information on concomitant medications taken within the past 30 days must be documented in the appropriate eCRF pages.

Concomitant medication use is captured inthe eCRF until the post-EOT visit.

Gastric protection agents are encouraged, as in guideline and consensus statements, especially for patients deemed to be at risk for gastrointestinal bleeding (20). The use of esomeprazole is *recommended* as it can be administered in combination with edoxaban without dose adjustment.

Medications listed below are allowed with the following *restrictions*:

- In the VKA-based regimen, study ASA isallowed if dose 100 mg once-daily
- In the edoxaban-based regimen, edoxabari dose reduction to 30 mg once-daily is required during concomitant use **with** certain P-gp inhibitors(please refer to local SmPC or to the IB, as applicable); In EU countries, according to SrnPC concomitant use of edoxaban with. cyclosporine, dronedarone, erythromycin, or ketoconazole requires dose requction to 30 mg once-daily. Concomitant use of edoxaban with *quinidine. verapamil. or amiodarone* does *not require* dose reduction.

5.10.1. Prohibited Medications

The following drug·s **are not permitt d** during the treatment period:

- Anticoagulants, other than the assigned edoxaban or VKA, by any route (with the exception of parenteral agents used to treat a new clinical event, such as acute coronary syndrome, or as a bridge when starting or resuming the assigned edoxaban or VKA);
- In the edoxaban-based regimen, concomitant treatment with ASA;
- Fibrinolytic agents, unless required to treat a new clinical event, such as acute MI, PE, or stroke, in which case the risks and benefits of such treatment should be considered and, if given, the assigned edoxaban or VKA should be temporarily discontinued;

- Chronic use (i.e., for 2:: 4 days/week) of oral or parenteral non-steroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 (COX-I) and cyclooxygenase-2 (COX-2) inhibitors. Study ASA is permitted as pre-defined for the VK.A-based regimen only. Use of NSAIDs via other routes (e.g., topical, inhaled, intranasal, intraocular, etc.) is not restricted;
- lnvestigationalarugs (otfier tfian tfie randozyuzed study treatment regimen).

Subjects on these drugs at the time of randomization are excluded from the study. After randomization, concomitant use of these drugs will require a study medication interruption. All study medication interruptions must be captured in the eCRF. After completion of the course of therapy with the prohibited concomitant drug, the interrupted study medication should be resumed.

6. STUDY PROCEDURES

The study is divided into a screening period, a treatment period and an observational post-treatmentfollow-up period. Subjects with an OAC indication for AF for at least 12 months who have undergoneeither elective or urgent PCI with stent placement successfully, are evaluated for potential participation in this study (included in pre-screening).

A tabular summary of the visit schedule for the study is provided in Appendix 17.9. All medications used in the study regimens are provided by the Sponsor and details on drug accountability are provided in Section 5.9.7.

6.l. Screening period (Pre-screening, Randomization / Baseline and Discharge)

Subjects will undergo study procedures only after the IC is signed and IC may only be obtained after the successful PCI procedure, when subject is considered eligible and when randomization is envisioned. Subjects who meet all inclusion criteria and none of the exclusion criteria may be randomized (Section 4.1.1and 4.1.2).

It is anticipated that most subjects have the described pre-screening procedures as part of standard of care outside the auspices of this study. Any protocol-specified study screening procedures/tests which are not part of standard of care need to be conducted after the subject signs the IC and before randomization.

6.1.1. Pre-screening

The following activities and/or assessments are performed at/during study screening:

- A re-check that the subject meets all of the inclusion criteria and none of the exclusion criteria (see Section 4.1);
- Last local laboratory test results, done post-index PCI:
  - Estimated CrCL (according to the Cockcroft-Gaultformula, see Appendix 17.6),

    Hemoglobin (Hgb),
  - platelet count, and
  - WBC (with differential if elevated).
- Checking the last available INR value (pre-:-randomization), done within the past 24 hours; INR must be :S 2.5

6.1.2. Baseline/ Randomization - Day 1

Prior to randomization:

- After contacting the IXRS, the Investigator provides the following information to the IXRS:

- Confirm tion written IC has been obtained;
- Confirmation subject fulfills all inclusion and none of the exclusion criteria;

  Demography (age, body weight and gender);

  Clinical presentation (ACS or stable CAD);
- Last value of estimated Creatinine clearance (CrCL);
- INR value prior to randomization;

  Usage of a P-gp inhibitor that requires an edoxaban dose reduction (according to local edoxaban SmPC or IB as applicable);
- Documentation of P2Y12 inhibitor other than clopidogrel and pre-declaration of the P2Y12 inhibitor to be prescribed (i.e., prasugrel, or ticagrelor);
- Pre-declaration of the intended duration of ASA (100 mg once-daily) therapy (I - 12 months), if randomized to the VKA-based regimen; Please consider subject's medical history including components of the CHA2DS2-VASc score, HAS-BLED score (Appendix 17.5);

Randomization:

- If the reported INR::; 2.5 and reported CrCL 15 mL/min, the IXRS accepts subject's eligibility and assigns the following:
  - subject identification number
  - the randomized treatment regimen
  - presence of edoxaban dose reduction requirement
  - kit numbers of the medications to be used
- The day of randomization will be Day 1.
- Urine sampling for pregnancy testing for women of childbearing potential (related to women who are pre-menopausal) (local laboratory)

Immediately after randomization:

The following activities are done after randomization and recorded in eCRF:

- Collection of blood samples for the following central laboratory tests:
  - Safety samples for: liver function, serum chemistry, hematology and INR

  The samples are processed and sent to the central laboratory (Section 9.6 and 8.2, respectively).

- The assigned treatment regimen and the proper daily dosing is explained to the subject including confirmation that the subject understands the proper daily dosing;
- Collection of a 12-lead ECG recording (see section 9.8). The last post-index PCI ECG recorded before randomization can be used;
- Collection of the re- and _Rost-angiograms for the indeX=P_CL(se e, section 10.1);
- For subjects randomized to the edoxaban-based regimen:
  - Administer the first dose of edoxaban and of study P2Y12 inhibitor according to Section 5.3.2 and 5.5.2, respectively.
- For subjects randomized to the VKA-based regimen:
  - Administer the first dose of VKA, of study P2Y12 inhibitor and of ASA according to Section 5.4.2, 5.5.2 and 5.6.2.

At hospital discharge or at the outpatient clinic:

- Dispensation of assigned study medication and of the medication log to the subject; Medication may be distributed to patients in an unbranded bag for convenience.
- Instruction is provided to the subject to bring all study medications including anticoagulant and antiplatelet medications to each visit as well as the filled in medication log;
- Schedule the next.on-site visit through the IXRS (i.e. Visit 2 at 1 Month).

Information to be recorded in the eCRF:

- The following information is recorded in the eCRF:
  - Th date and timing of the first'dose of each study medication
  - All determined INR values and dose adjustments to reach target INR range of 2.0- 3.0 inclusive;
  - Significant physical findings under medical history;
  - Medical history including components of the CHA2DS2-VASc score, HAS-BLED score (Appendix 17.5) and past history of bleeding events;
  - All medications the subject was taking within 30 days prior to randomization (including medications given befo e and during the PCI procedure) see section 5.10;
  - Obtain a copy of the PCI procedure report and record information about index-procedure (e.g. but not limited to vascular access, lesions treated, stents used, procedure result);

- Local laboratory cardiac enzymes *before* and *after* index-PC!, if available (the closest to the index-PC! procedure and the most recent prior to randomization, respectively).
  Consider collecting (it is not necessary to wait for these test results before randomizing the subject):
  - Cardiac troponin (cTn)
  - creatinase MB isoform (CK-MB)
- Last local laboratory test results , done post-index PCI:
  - Hemoglobin (Hgb)
    Platelet count
  - WBC (with differential if elevated)
    Total bilirubin (if elevated, determine conjugated/unconjugated bilirubin fraction)
- Local laboratory test results, if available (the closest to the index-PC! procedure).
  - Cholesterol, total
  - Triglycerides
- Vital signs

6.2. Treatment Period

Dates for all visits following the randomization visit are calculated to occur in relation to the randomization visit, with the <late of randomization being Day 1.

6.2.1. On-site Visits: 1, 3, 6, and 9 Months (±7days) orunscheduled

The following activities and/or assessments are performed at each on site visit:

- Collection of blood samples for the following central laboratory tests:
  - Safety samples for: liver function, serum chemistry, hematology, INR.

  The samples are processed and sent to the central laboratory (Section 9.6).
- Urine sampling for pregnancy testing for women of childbearing potential (related to women who are pre-menopausal) (local laboratory)
- Dispensation of the assigned study medication and of the medication log to the subject; Medication may be distributed to patients in an unbranded bag for convenience.
- The assigned treatment regimen and the proper daily dosing is explained to the subject including confirmation that the subject understands the proper daily dosing;
- Collection of a 12-lead ECG recording (see section 9.8);

- Local laboratory INR are determined for subjects randomized to VKA;
- Instruction is provided to the subject to bring all study medications to each visit, including edoxaban or VKA, P2Y12 antagonist, and ASA if applicable as well as the filled in medication log;
- The following information is recorded in the eCRF:
  - Local laboratory CrCL;
  - Kit assignment for edoxaban or VKA, P2Y12 antagonist, and ASA study medications as needed;
  - Discontinuation of ASA treatment (1-12 months), according to pre-declaration at randomization
  - Next on-site visit is scheduled (i.e. Visit 4, 3 Months; Visit 7, 6 Months; Visit 10, 9 Months).
- The following information is recorded in the eCRF:
  - For subjects on VKA, all determined INR values and dose adjustments;
  - Any interruptions or dose adjustments of all study anticoagulant and antiplatelet dnigs with the date of last dose and the date of the first dose of resumption of drug (Section 5.7). Record this for each of the following separately:
    - Edoxaban or VKA
    - P2Y12 antagonist
    - ASA
  - Date of the final dose of ASA in line with pre-declaration at randomization;
  - Concomitant medications;
  - All endpoints and all AEs experienced by the subject since the last visit.
    - Endpoint and other event reporting occur throughout the study as soon as site personnel learn of the endpoint/event. In case of a suspected study endpoint, an additional assessment for subject compliance to the assigned regimen must be performed.
    - For subjects who experience a stroke event after randomization, the Investigator evaluates the residual disability by modified Rankin score 3 months after the onset of stroke (see Section 0).
    - Any treatments (drug and non-drug) given for endpoint events and AEs since the last visit.

Any h9spitalizations, coronary or vascular intervention or major coronary surgery (e.g. PCI or CABG procedures) since the last visit.

Data on non-protocol driven outpatient physician or nurse visits, emergency room visits, or the use of long-term care, rehabilitation, or skilled nursing facilities related.to bleeding, srrol<e-;SEE, myocaraiarinfarction, or stent thrombosis since the last visit.

- Vital signs
- Accountability of unused tablets of dispensed for edoxaban, P2Y12 antagonist, and ASA;

6.2.2. Telephone Assessments: 2, 4, 5, 7, 8, 10 and 11 Months(± 7 days)

The following assessments are performed during each telephone assessment:

- The following information is recorded in the eCRF:
  - Documentation of the most recent INR for subjects randomized to VKA;
  - Any interruptions or dose adjustments of all study anticoagulant and antiplatelet drugs with the date of last dose and the date of the first dose of resumption of drug (Section 5.7). Record this for each of the following separately:

    Edoxaban or VKA

    P2Y12 antagonist

    - ASA
  - Concomitant medications;
  - All endpoints and all AEs experienced by the subject since the last visit/telephone assessment.

    Endpoint and other event reporting will be done throughout the study as soon as site personnel learn of **the** endpoint/event. In case of a suspected study endpoint, an additional assessment for subject compliance to the assigned regimen must be performed.

    Any treatments (drug and non-drug) given for endpoint events andAEs since the last visit/ telephone assessment.
  - Self-conducted pregnancy tests for women of childbearing potential (related to women who are pre-menopausal)

- Next telephone assessment or on-site visit is scheduled, as applicable.

6.2.3. On-site Visit: 12 Months± 7 days (End-of-Treatment)

The following will be performed for all subjects aJ the End-of-Treatment Visit (EOT):

- Collection of blood samples for the following central laboratory tests:
  - Safety samples for liver function, serum chemistry, hematology and INR

  The samples are processed and sent to the central laboratory (Section 9.6).
- Urine sampling for pregnancy testing for women of childbearing potential (related to women who are pre-menopausal) (local laboratory)
- Dispensation of the transition study medication;
- The transition medication and the proper daily dosing is explained to the subject including confirmation that the subject understands the proper daily dosing;
- Collection of a 12-lead ECG recording (see section 9.8).
- Local laboratory INR are determined for subjects randomized to VKA;
- The following information is obtained or recorded in the IXRS:
  - Local laboratory CrCL;
  - Transition from assigned study regimen to an appropriate therapy (Section 5.3.3 and 5.4.4)
- The following information is recorded in the eCRF:
  - For subjects on VKA, all determined INR values and dose adjustments;
  - Date and time of the final dose for each of the study drugs;
  - Any interruptions or dose adjustments of all study anticoagulant and antiplatelet drugs with the date of last dose and the date of the first dose of resumption of drug (Section 5.7). Record this for each of the following separately:
    - Edoxaban or VKA
    - P2Y12 antagonist
    - ASA
  - Concomitant medications;
  - All endpoints and all AEs experienced by the subject since the last visit.
    - Endpoint and other event reporting occur throughout the study as soon as site personnel lefill} of the endpoint/event.

In case of a suspected study endpoint, an additional assessment for subject compliance to the assigned regimen must be performed.

For subjects who experience a stroke event after randomization, the investigator evaluates the residual disability by modified Rankin score at the time of discharge from the hospital csee Sectioff 0 \-.

Any treatments (drug and non-drug) given for endpoint events and AEs since the last visit.

Any hospitalizations, coronary or vascular intervention or major coronary surgery (e.g. PCI or CABG procedures) since the last visit.

Data on non-protocol driven outpatient physician or nurse visits, emergency room visits, or the use of long-term care, rehabilitation, or skilled nursing facilities related to bleeding, stroke, SEE, myocardial infarction, or stent thrombosis since the last visit.

- o Vital signs
- o Accountability of unused tablets of dispensed for edoxaban, $P2Y_{12}$ antagonist, and ASA

- For subjects still on edoxaban or VKA, the final on-site visit is scheduled (i.e. Visit 14, 1 Month post-EOT);
- The EOT visit is performed for subjects who have a premature discontinuationof their assigned OAC-based regimen or who have modified their IC after randomization with full withdrawal of IC (see details section 6.5).For these subjects, the scheduling of the EOT remains unchanged (i.e. 12 months± 7 days). In such cases, the EOT visit is the end-of-study visit/contact.

6.2.4. Additional Visits/Assessment in the VK.A-based regimen

For subjects randomized to the VKA-based regimen, INR management may be performed by the Investigator, the subject's primary care physician or other private physician, or at a specialized anticoagulation clinic or patient self-monitoring. Documentation of all INR values must be maintained, including INR tests performed outside oflnvestigator'ssite. It is the responsibility of the Investigator or designee to enter all INR results into the eCRF.

The Investigator or designee will measure or collect (by email or fax) the subjec 's INR value(s) and VKA dose information **at least every month.** Separate documents provided to the sites will inform the Investigator of the recommended frequency of INR monitoring.

For Investigators who are managing INR for subjects assigned to VKA, unscheduled site visits are pennissible to achieve and maintain an INR in the target therapeutic range (2.0 - 3.0). The procedures performed at such an unscheduled

visit are identical to those described above for regular on site visits (see section 6.2.1).

6.2.5. Missed Follow up Visits

Every effort should be made to ensure subjects return for their on-site visits. If the sub-Jecr'isu naole to return for an on-site visit-;-tfie lnves tlgator, or des1gnee, mus document _in the patient record the reason the subject was unable to complete the visit. The Investigator should also make every effort to contact the subject, within the visit window, to collect the subject's vital status as well as information related to potential adverse events, safety data, and hospitalizations.

6.3. Post-treatment Period

6.3.1. On-site Visit: 1 month post-EOT (± 7 days)

All subjects on edoxaban or VKA at 12 months (EOT visit), have a visit planned 30 days thereafter.

Subjects who prematurely discontinued their assigned OAC will not require an additional follow-up visit or telephone contact after the End of Study Visit apart from patients withdrawn due to AEs (see section 4.3.1 and 43.2).

The following wUl be performed at the post-EOT visit:

- Record targeted concomitant medications;
- Collection of a 12-lead ECG recording (see section 9.8);
- Vital signs;
- Record all endpoints and all AEs experienced by the subject since the la,st visit.
    - Endpoint and other event reporting (including hospitalization) will be done throughout the study as soon as site personnel learn of the endpoint/event; For subjects who experience a stroke event after randomization, the Investigator will evaluate the residual disability by modified Rankin score at the time of discharge from the hospital (see Section 17.7).
    - Record any treatments (drug and non-drug) given for endpoint events and AEs since the last visit.
    - Record any hospitalizations, PCI procedures, and CABG procedures since the last visit.

6.4. Protocol Deviations

The Investigator conducts the study in compliance with the protocol agreed to by sponsor and, if required, by the regulatory authority(ies) and by the EC.

Actions taken to eliminate immediate subject hazard(s) that deviate from any protocol procedures are marked/ flagged as a deviation. The sponsor and site monitor must be notified of all intended or unintended deviations to the protocol (e.g., inclusion/exclusion criteria, dosing) on an expedited basis. The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol and notify the EC of any protocol deviations in accordance with local procedures.

Even if a subject was ineligible or inadvertently received the incorrect drug or dosage, discontinued or interrupted the assigned treatment regimen, or refused to further undergo on-site visits, clinical follow-up data should still be collected up to 12 months after randomization (EOT).

6.5. Modification of IC after Randomization

Subjects are scheduled to have regular study contacts every month until the 12-month EOT visit is completed.

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

This protocol makes a distinction between request to discontinue (1) any or all study medication, (2) on site visits, (3) telephone contacts, (4) collection of clinical follow-up data, (5) collection of vital status and (6) full withdrawal ofIC.

All subjects are followed for 12 months irrespective of changes in the antithrombotic regimen. Henceforth, during interruption or following discontinuation of study medication, subjects continue to have regular study visits or telephone assessments until the 12-month EOT visit is completed.

If the subject cannot return for an in-person visit, a telephone visit is scheduled unless subject requests not to be contacted by telephone. Collection of available clinical data or vital status, either at the interventional centei;, at the referring hospital, with the general practitioner,or the municipal registries continues unless explicitly disallowed by subject.

Collected data up to the date of full withdrawal ofIC are used in the final analysis.

Records in the eCRF document modifications to the IC as detailed above (incl. level and date of modification or withdrawal).

6.5.1. Subjects Lost to Follow-Up

All subjects should be encouraged to return for protocol-required on-site visits or telephone assessments for evaluation during the clinical follow-up. If a subject is unable to return for a clinic visit, subject should be contacted by telephone.to obtain subject required information. All attempts should be documented in the

source documents. If the subject does not respond to telephone calls, then the Investigator must send a certified letter to the subject. Only after failing to contact the subject at.the final follow-up visit will the subject be considered lost to follo - up after last contact except for mortality if available via municipality registries. It must be a high priority to obtain at1east survival data on all subjects lost to follow-up. When a subject is lost to follow-up a study End-of-Study Form is completed.

6.6. End of Trial Definition

All subjects on OAC study medication (edoxaban or VKA) at 12 months, have a contact planned 1 month after the EOT visit, to collect data on targeted concomitant medications, SAEs, and other events of interest. The final contact is either the scheduled EOT visit at 12 months or the post-treatment follow-up visit scheduled at 13 months. The study completion is reached as soon as the final contact of the last subject is performed in all centers and in all participating countries.

7. OUTCOME ASSESSMENTS

7.1. Primary Endpoint

The primary endpoint is the composite of major or clinically relevant non-major bleeding (MCRB) defined according to the ISTH-defined bleeding definitions, analyzed as time to first occurrence of any component.

7.2. Secondary Exploratory Endpoints

The secondary endpoints are defined as:

- Main efficacy endpoint (MEE), defined as the composite of cardiovascular (CV) death, stroke, systemic embolic events (SEE), myocardial infarction (MI) and definite stent thrombosis.
- Net clinical benefit (NCB), defined as the composite of CV death, stroke, SEE, MI, definite stent thrombosis and ISTH-defined major bleeding.
- Main thromboembolic event, defined as composite of cardiac or thromboembolic death (thromboembolic death considered to be thromboembolic in origin (including thromboembolic stroke, pulmonary embolism, any other systemic embolism), ischeniic stroke, SEE, MI and definite stent thrombosis.

  ISTH-defined major bleeding
- Any bleeding defined as the composite of major, clinically relevant non-major and minor bleeding (ISTH definition)

  Symptomatic intracranial hemorrhage (ICH)
- Composite of stroke and SEE

  Composite of all-cause death, stroke, SEE, MI and definite stent thrombosis

  Composite of CV death, MI and definite stent thrombosis
- The single components of the composite primary and secondary endpoints mentioned above are explored, as well as specific subcategories (e.g., hemorrhagic, ischemic and undetermined stroke)

  Safety parameters such as (serio us) adverse events, laboratory parameters, ECG and vital signs.

All secondary endpoints are analyzed as time to first occurrence of any of its components.

Bleeding events are also classified acco ding to Bleeding Academic Research Consortium (BARC) and Thrombolysis in Myocardial Infarction (TIMI) classifications for descriptive purposes only. All suspecte9 bleeding events are adjudicated by the CEC in a blinded manner.

All events are also sub-categorized into fatal and non-fatal.

For all endpoints blindly adjudicated by the CEC, the CEC's interpretation prevails and is used in the statistical analyses.

7.3. Endpoint definitions

All suspected endpoint events are adjudicated by an independent CEC (see section 17.1.2) without knowledge of the actual assigned treatment. The adjudication criteria are mentioned below. Further details on these definitions and how they will be assessed are provided in the CEC Charter. Th requirements for collecting and submitting the source documents for appropriate adjudication of the reported primary and secondary endpoint events will be provided to the sites/Investigators separately in the Study Operations Manual.

For all endpoints blindly adjudicated by the CEC, the CEC's interpretation prevails and is used in the statistical analyses.

7.3.1. Bleeding

Bleeding will be classified according to the 18TH definitions (see section 17 .3). Bleeding events will also be classified according to BARC (14) and TIMI (21, 22) classifications for descriptive purposes only.

7.3.2. Components of MEE

The following endpoint definitions will be applied:

CV death, defined as cardiac or vascular death according to Academic Research Consortium (ARC) (23) ..

- Thromboembolic death (thromboembolic death considered to be thromboembolic in origin (including thromboembolic stroke, pulmonary embolism, any other systemic embolism), defined as CV death excluding fatal bleeding defined as BARC sub-category 5 (14).
- A stroke is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit in the distribution of a single brain artery that is not due to an identifiable nonvascular cause (i.e., brain tumor or trauma), and that either lasts at least 24 hours or results in death within 24 hours of onset (13). Stroke will be sub-divided into ischemic, hemorrhagic or indeterminate. Stroke is categorized in disabling and non-disabling stroke using the mRS score.

  TIA is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit in the distribution of a single brain artery, that lasts less than 24 hours and is not due to an identifiable non-vascular cause (i.e., brain tumor or trauma) and does not satisfy the stroke definition above. (13)

  An SEE is defined as an arterial embolism resulting in clinical ischemia, excluding the central nervous system (CNS), coronary and pulmonary arterial circulation (13).

  Spontaneous MI according to Universal MI definition (24) and periprocedural MI according to the SCA! MI definition (25)

Stent thrombosis according to ARC (23)

7.3.3. Other

lntracranial hemorrhage is a sub-category of ISTH major in a specified critical organ, to be determined by the CEC.

8. PHARMACOKINETIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Variable(s)

Not applicable.

8.2. Non-genetic biomarkers and Exploratory Variable(s)

Not applicable (please refer to section n 2)

9. SAFETY ASSESSMENTS

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

9.1. Adverse Events (AEs)

9.1.1. Definitions

9.1.1.1. Adverse Event (AE)

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 unfavourable 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.

9.1.1.2. Unexpected Adverse Event

An unexpected AE (uAE) is an AE, the nature or severity of which is not consistent with the reference safety information of any of the study medication. 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. The investigator can provide his judgment on the expectedness/unexpectedness of a reported AE to the sponsor and this will be taken into account for the sponsor's judgment of expectedness. However, the final determination of expectedness is the responsibility ofDSE and not the investigator.

9.1.1.3. Expected Adverse Event

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

9.1.1.4. Serious Adverse Event (SAE)

An SAE or reaction is any untoward medical occurrence that at any dose:

- results in death.
- is life-threatening.
  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.
- requires inpatient hospitalisation or prolongation of existing hospitalisation.
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.

OR

- is any other medically important condition (see below).

Note: Medical and scientific judgement 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 hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE.
- Treatment requiring hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.

9.2. Classification for AE assessment

9.2.1. Severity of Adverse Events

The severity of an AE is graded as follows:

Mild: Discomfort noted, but no disruption of normal daily activity.

Moderate: Discomfort sufficient to reduce or affect normal daily activity.

Severe: Inability to work or perform normal daily activity.

9.2.2. Relationship of Adverse Events

The Investigator should assess causal relationship between an adverse event and the assigned anticoagulant-based regimen (i.e., edoxaban-based or VKA-based) on the basis or his/her clinical judgment and the following definitions. The causality assessment should 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 the assigned anticoagulant-based regimen 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).
  The AE follows a reasonable temporal sequence from the assigned anticoagulant-based regimen administration, and is a known reaction to any of the study medications (i.e. the components of each

study regimen) under study or its chemical group, or is predicted by known pharmacology.

- 2 = Not Related:
  The AE does not follow a reasonable sequence from the assigned anticoagulant-based regimen administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study; concurrent diseases affd concomitant medications).

9.2.3. Action Taken Regarding the Assigned Antithrombotic Regimen

For each drug of each antithrombotic regimen (either, edoxaban and clopidogrel in the edoxaban-based regimen or VKA, P2Y12 inhibitor and ASA in the VKA-based regimen), the action taken after an AE must be recorded in the eCRF as delineated below:

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

2 = Drug Withdrawn: Permanently stopped.

3 = Dose Reduced: The dosage was reduced.

4 = Drug Interrupted: Temporarily stopped.

5 = Dose Increased: The dosage was increased.

9.2.4. Other Action Taken for Event

1 = None: No treatment was required.

2 = Concomitant medication required: Prescription and/or over-the-counter medication were requir d 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.

9.2.5. AE Outcome

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

2 = Recovered/Reso lved 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

Tne 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.

9.3. AEs of Special Interest

9.3.1. Combined Elevations of Aminotransferases and Bilirubin

There was no clinically concerning signal of drug-induced liver injury associated with edoxaban based on the extensive global phase 3 experience involving over 34,100 edoxaban subject-years exposure (with median drug exposure of ~2.5 years among ~14,000 edoxaban subjects). However, there will be ongoing monitoring of hepatic events, including combined elevations of aminotransferases and bilirubin (ALT or AST> 3 x ULN with simultaneous TBL > 2 x ULN), particularly those without evidence of cholestasis (ALP 2: 2xULN is considered evidence of possible cholestasis) and without alternative etiology for hepatocellular damage.

Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, should always be reported to the Sponsor as soon as possible following the procedures outlined in Section 9.5 for SAE reporting.

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

9.3.2. 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,.

If any study subject or their partner becomes or is found to be pregnant while receiving, or within 30 days of discontinuing the investigational product, the Investigator should contact the Medical Monitor to discuss subject management and receive further information. 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 fori:n).

If it is the partner, rather than the subject, who is found to be pregnant, the Exposure in Utero Reporting Form should be completed with the subjects' identification number, and year of birth. Details regarding the partner should be entered in the narrative section of the Exposure in Utero Reporting form if a consent of the trial subject's partner has been obtained bythe Investigator.

If the pregnancy is to be terminated, the anticipated date of termination should be reviewed. 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 a 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.

9.4. Timing of Adverse Event Reporting

All AEs must be recorded and reported from the stated starting point of the clinical trial (immediately after signing IC) including AEs taking place during the administration of other drugs. Even if the subject has not yet received the investigational study regimens, 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 anticoagulant-based regimen 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 anticoagulant-based regimens, this study will report all (S)AEs occurring after the subject signs the IC and up to 30 days after the last dose of the assigned anticoagulant-based regimen, whether observed by the Investigator or reported by tlie subject. All AEs will be recorded on the AB/Outcome eCRF page and include:

- Any components of the study endpoint assessments (see Section 7);
- AE that meet seriousness criteria (see Section 9.2.1);
- AE that result in interruption or discontinuation of the assigned anticoagulant-based regimen;
- AE that meet the criteria for AE of special interest (see Section 9.3);
- 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 par1 of medical history.

All SAEs are to be reported according to the procedures in Section 9.5.2 below. 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 availabl,,. 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 serious adverse event (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: 9.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

In case of an occurrence of an (S)AE, the Investigator applies the following rules:

- Ensure appropriate medical treatment and decide whether to discontinue or interrupt any of the study 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 po sible.
- 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.

9.5.2. Notifying Regulatory Authorities, Investigators and IRB/IEC,

Detailed SAE processing, distribution and reporting will be laid out in sponsor's SAE Flow Plan.

Sponsor and/or ARO/CRO will inform Investigators, IRBs (Institutional Review Board)/IECs (Independent Ethics Committees), and regulatory authorities of any Suspected Unexpected Serious Adverse Event Reactions (SUSARs) occurring in the study or other sponsor studies of the investigation a1product (excluding waived study endpoint events per Section 6.6), as appropriate per local reporting requirements.

In the European Bnion countries, it is the Sponsor's i esponsibility io1epo SUSARs to regulatory authorities and IECs.

Study endpoints are clinically anticipated events in AF subjects receiving antithrombotic therapy and will be periodically reviewed by the DSMB in a blinded manner to ensure prompt identification of any clinically concerning safety issues.

9.6. Clinical Laboratory Evaluations

Refer to the Laboratory Manual for detailed instructions of sample collection, storage, and shipment. The results will be reviewed and compared to the central laboratory's normal ranges. The visits at which these samples will be collected are shown irt the schedule of assessments (Appendix 17.9).

The following safety laboratory evaluations are performed in individual blood samples.

- Liver Function Panel
    - Total bilirubin (conjugated/unconjugated.performed when total serum bilirubin 2: 2 mg/dL)
    - Alanine transaminase (ALT)
    - Aspartate transaminase (AST)
    - Alkaline phosphatase (ALP)
- Serum Chemistry Panel
    - Creatinine
- Hematology Panel
    - White blood cell (WBC) count with differential ifelevated
    - Hemoglobin
    - Platelet courit
- INR
- Urine Sampling (only at baseline and follow up for pregnancy testing). Pregnancy tests will be provided for female patients with childbearing potential (related to women who are pre-menopausal) to be performed at home in case of visits by phone.

All other assessment 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 re uire monitoring according to local routine.

9.7. Vital Signs

The following parameters are recorded for vital signs:

- Blood pressure (BP), sitting diastolic and systolic BP
- Weight
- Height (only at baseline)

9.8. Electrocardiograms

Twelve-lead ECG are collected according to the schedule of assessments (section 17.9). Investigational sites will utiliz-e local ECG equipment and record pertinent information in the eCRF while preserving all recorded ECG tracings as subject source documentation.

9.9. . Physical Findings

The Investigator or a licensed team member performs targeted physical examination according to the schedule of assessments. This physical examination cons_ists of assessment of each of the relevant (including but not limited to cardiac, neurologic, pulmonary, GI) major body systems. In order to be able to detect any renal impairment, the Creatine Clearance will be calculated. In addition, All information needed for the calculation will be collected in the eCRF. Any clinically significant findings must be recorded in the eCRF under.medical history at baseline and under AB/Outcome until the subject's final contact.

10. OTHER ASSESSMENTS

10.1. Coronary angiograms

The pre- and post-index PCI coronary angiograms are recorded according to the standard of care.

10.2. Hospitalisations

In addition to the standard SAE data collected for hospitalisation as described in Section 9.1.1.4, additional data will be collected for hospitalisations that are reported for one of the following reasons:

- Bleeding
- Stroke
- SEE
- Myocardial infarction
- Stent thrombosis

Data on length of hospital stay (admission and discharge dates), admission unit (e.g. ICU), admission diagnosis and discharge status will be collected for any of the above hospitalisations.

In addition, data on non-protocol driven outpatient physician or nurse visits, emergency room visits, or the use of long-term care, rehabilitation, or skilled nursing facilities related to bleeding, stroke, SEE, myocardial infarction, or stent thrombosis will be collected throughout the study.

11. STATISTICAL METHODS

11.1. Analysis Sets

11.1.1. Intention-to-treat analysis set

The Intention-to-treat Set (ITT) consists of all randomized subjects irrespective whether they received a single dose of the randomized study regimen or no.

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. Th 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 Analysis Set (mITT) 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 randomizedsubjects 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
    - No stent placement
    - No successful PCI (see section (definjtion))
    - Planned further (staged) PCI
    - NoAF
    - Known contraindication for OAC
- An unequivocal violation of the exclusion criteria

The list of major violations will be finaljzed before data base 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 t e date and time of first intake of study edoxaban or study VKA.

11.1.4. Safety analysis set

The Safety (SAF) Analysis Set 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 tlie incorrect arug(s) or aosage during the entire study, in which case the subject will be grouped accorqing to the treatment actually received. The reference date for consideration of endpoints is the date of first study.medication intake.

Note: This SAF analysis set is identical to the mITT analysis set and 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 2'.: 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 variab)es, 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 deviatio andother dispersion statistics will have two more decimal places; and minimum and maximum values will be displayed to the same number of decimai 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 (ie 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.

The statistical data analysis will be performed by a CRO under the guidance of the study biostatistician using SAS Version 9.3 or higher.

Definition of terms:

'Overall Study Period': This period is <;iefined as the time from the reference date (date and time of randomization or date and time of first study edoxaban or study VKA intake) to Day 365.

'Qvemll Study P-er-iod =I= 30 da ys': T his perfod is defined as the time :from thv reference data (date and time of randomization or date and time of first study edoxaban or study VKA intake) to Day 395.

'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.

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 qf study edoxaban or study VKA.

The main analyses of adjudicated primary and secondary exploratory endpoints (Section 7:1 and 7.2, 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 medication (edoxaban, VKA, P2Y12 antagonist, and ASA) will be SllID;Jllarized using descriptive statistics by treatment regimen for the mITT, PP and SAF analysis sets. Interruptions and permanent discontinuations (see Section 5.7) will be summarized by treatment group for the same nalysis sets.

The time in therapeutic range (TTR) (INR: 2.0 to 3.0, inclusive) will be estimated for each subject randomized to the VKA-based antithrombotic regimen using the interpolation method of Rosendaal (26).

11.4. Statistical Analysis

For each of the primary and secondary exploratory endpoints, appropriate summary statistics (e.g. event rate) including 95% 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 stratificat'ion factors from the randomization (IXRS) 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.

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

For time to first event analyses based on the ' overall study period', cumulative event rates over time are summarized using the Kaplan-Meier method.

11.4.1. Analysis of the prim ry endpoint

The primary endpoint is defined as the composite of major or clinically relevant non-major bleeding (MCRB) defined according to the ISTH-defined bleeding definitions (see section 7.3).

There are two primary hypotheses for the primary endpoint_to be tested in this study.

- The edoxaban-based antithrombotic regimen is non-inferior to the VKA-based antithrombotic regimen with regards to MCRB.
- The edoxaban-based antithrombotic regimen is superior to the VKA-based antithrombotic regimen with regards to MCRB.

These two hypotheses are tested in a hierarchical manner, non-inferiority followed by superiority to control the type-I error rate, with adequate power for each of the two hypotheses.

11.4.1.1. Test for non-inferiority

The *primary analysis to show non-inferiority* will be based on first occurrence of an (adjudicated) MCRB that occurred during the 'overall study period' for all subjects belonging to the ITT analysis set and applying the aforementioned statistical method. The edoxaban-based regimen will be considered non-inferior to the VKA-based regimen, if the upper boundary of the two-sided 95% CI for HR falls below 1.20.

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', 'overall study period+ 30 days' will be presented but should be interpreted in a more descriptive way. Results for other combinations of analysis sets and analysis periods may be presented if considered necessary.

11.4.1.2. Test for superiority

The *primary analysis to show superiority* will be basec,1 on first occurrence of an (adjudicated) MCRB that occurred during the 'overall study period' for all subjects belonging to the ITT analysis set and applying the aforementioned statistical method. The edoxaban-based regimen will be compared with the VKA-based regimen for superiority only if the non-inferiority of the edoxaban based regimen is established first. The edoxaban-based regimerrwill be considered superior to the VKA-based regimen, if the upper boundary of the two-sided 95% CI for HR falls below 1.00.

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 dcise + 30 days', 'overall study period + 30 days' will be presented but should be interpreted in a more descriptive way. Results for other combinations of analysis sets and analysis periods may be presented if considered necessary.

11.4.2. Analysi of the secondary exploratory endpoints

The *main analysis for all secondary exploratory 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 pplying the aforementioned statistical method.

There wiII be no formal statistical testing for secondary exploratory endpoints. HRs, CI and p-yalues 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', 'overaII 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 Analysis

11.4.3.1. Pharmacokinetic Analyses

Not applicable (there will be a separate sub-study protocol) (please refer to section 17.2).

11.4.3.2. Pharmacodynamic Analyses

Not applicable.

11.4.3.3. Biomarker Analyses

Not applicable (there will be a separate sub-study protocol) (please refer to section 17.2).

11.4.3.4. Pharmacogenomic Analyses

Not applicable.

11.4.4. Health Economics Outcome Research (HEOR) Analyses

Not applicable (there will be a separate sub-study protocol) (please refer to section 17.2).

11.5. Safety Analyses

11.5.1. Adverse Event Analyses

Adverse events meeting the criteria defined in Section 9.1 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.

The AE analysis will be based on the SAF analysis set. 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% resp. 1% 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 9.1 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, including elevated liver enzymes and/or bilirubin, and the change from baseline will be summarized for the SAF analysis set by treatment regimen. 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.

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 for the SAF analysis set by treatment regimen. The number and percentages of subjects with abnormal vital signs while on study drug will be summarized by treatment regimen.

11.5.4. Electrocardiogram Analyses

The ECG evaluations at baseline, Month 1, Month 3, Month 6, Month 9, Month 12 and at FU visit will be summarized by treatment regimen. More details on the ECG analysis will be given in the SAP.

11.5.5. Physical Examination Analyses

p ys1ca exammat10n will only be performeo at tnebaselme v1s1t.

Counts and percentages of physical examination findings will be summarized by treatment regimen based on SAF analysis set.

11.6. Other Analyses

Details on the Syntax Score and hospitalisations analyses will be given 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 (incidence ofMCRB or MEE, or suspected related (S)AEs) on an ongoing basis in a unblinded manner to ensure a prompt identification of any safety issues 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 specifie in theDSMB charter.

11.9. Sample Size Determination

The sample size determination for the study was driven by requirements for testing superiority of the edoxaban-based regimen over the VKA-based regimen as described above.

The power calculation was based on a test using the Cox proportional hazards model and was performed with PASS version 14.0.4, with the module for two survival curves using Cox's proportional hazards model) under the ITT principle with a fixed follow-up time of 12 months (i.e., 365 days).

Based on a review of available safety data, the estimated one-year event rate of the primary endpoint (MCRB, i.e. ISTH major or clinically relevant non-major bleeding) under the VKA-based antithrombotic regimen is 24%-(13, 27, 28). The edoxaban-based antithrombotic regimen is anticipated to reduce the one-year incidence to 18% (a relative risk (RR) of 0.75). Under the assumption of an exponential distribution, the hazard ratio (HR) equals 0.7231.

The accrual of 2 x 712 evaluable subjects provides 80% power to demonstrate superiority of the edoxaban-based antithrombotic regimen over the VKA-based

antithrombotic regimen at a two-sided a=0.05. To compensate for loss-to-follow-up within 12 months, the final sample size is set at 2 x 750 subjects.

With this sample size, the study has 82% power to show non-inferiority (with a margin of 1.20) if the underlying HR is.0.88 at a one-sided significance level of 2.5%.

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IEC 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.

12.1. Monitoring and Inspections

The Sponsor, site monitors, 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., CRFs, source data, and other pertinent documents).

The monitor is responsible for visiting site(s) at regular intervals (as detailed in the Monitoring Plan) throughout the study to verify adherence to the protocol; completeness,.accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the CRFs 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 CRFs.

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.

TheInvestigator 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 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.

In the event that a regulatory authority informs the Investigator that it intends to conduct an inspection, sponsor shall be notified immediately.

12.2. Data Collection

The eCRF completion should be kept current to enable the monitor to review the subject's status throughout the course of the study. The eCRF is completed by the Investigator or qualified designee. Completed eCRFs are r viewed and e-signed by the Investigator (or by a sub-Investigator, with permission of the Sponsor).

12.3. 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, sponsor will inform all Investigators involved in the clinical study, ethics committees, and regulatory authorities of such

information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject orally 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 re aini n the study or no.

If the subject information is revised, it must be re-approved by EC. The investigator should obtain written IC to continue participation with the revised written information even if subjects are already informed of the relevant information orally. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised IC.

12.4. Data Management

Each subject will be identified in the database by a unique subject identification number as defined by the sponsor.

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications given to the CRO. Data on eCRF is vetted electronically by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. Dui-ing this review, subject data will be checked for consistency, omission.s, and any apparent discrepancies.

Data received from external sources such as centnd labs will be reconciled to the clinical database.

SAEs in the clinical database will be reconciled with the safety database.

12.S. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. -".\,ll persons authorized to make entries and/or corre_ctions on eCRFs will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's eCRF 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 conespondence.

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 sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing ICs, and supporting copies of source documentation as used for eCRFs completion. In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

- 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 IEC/IRB and Sponsor.
- Records related to the study medications delivered including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence.

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

Essential clinical trial documents (including case report forms) other than subject's medical files must be kept for at least 15 years after completion or discontinuation of the trial. 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. It is the responsibility of the sponsor to inform the Investigator/institution as to when the clinical trial documents no longer need to be retained.

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 DSE in writing of the new responsible person and/or the new location.

12.6. 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/EC correspondence and approvals, approved and signed ICs, 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. FINANCINGAND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with the sponsor or with ari authorized representative of sponsor. This agreement will include the financial information agreed upon by the p..arties

13.2. Reimbursement, Indemnity, and Insurance

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

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

14. PUBLICATION POLICY

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until one year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that sponsor and the executive committee has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the advice of company patent council and in accord with needs for subject protection.

15. STUDY ADMINISTRATIVE INFORMATION

15.1. 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. All protocol amendments will undergo the same review and approval process as the original _m-otocol. A subs tantial.protocol amendment may be implemented after it has been approved by the IEC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IEC within five working days. The sponsor will assure the timely submission of substantial amendments to regulatory authorities.

15.2. Address List

15.2.1. Sponsor

Daiichi Sankyo Europe GmbH
Zielstattstrasse 48
81379 Munich, Germany

15.2.1.1. DSE Project Leader

[redacted]

15.2.1.2. DSE Medical Expert

[redacted]

15.2.2. Academic Research Organizations

European Cardiovascular Research Institute (ECRI)
PO Box 2125, 3000 CC Rotterdam, The Netherlands.
[redacted]

Kompetcnznctz Vorhofflimmern e.V. (AFNET e.V.)
Mendelstr. 11, D-48149 Mtinster, Germany.
[redacted]

Cardialysis
Westblaak 98, 3012 KM Rotterdam, The Netherlands.

[redacted]

15.2.3. CRO

Chiltern International
37 bis rue de Villiers,
92200 Neuilly sur Seine,
France

15.2.3.1. CRO Medical Monitor

[redacted]
Canada Square Office House, Ganz u. 12-14, 4, Budapest, Hungary, H-1027
[redacted]

15.2.3.2. CRO Project Manager

[redacted]

15.2.4. Drug Safety

15.2.4.1. DSE

[redacted]

15.2.4.2. CRO

[redacted]
171 Bath Road, Slough,
Berkshire, SL1 4AA, United Kingdom
[redacted]

15.2.5. Interactive Web Voice Response System (IXRS)

Endpoint Clinical, Inc.
55 Francisco Street, Suite 200
San Francisco, CA 94133

[redacted]

15.2.6. Bioanalytical Laboratory

Europe (except Ukraine)
Medical Laboratory SYNEVO
Marynarki Polskiej Str.163
(in building C200 office)
Gdansk, POLAND
80-868

[redacted]

Ukraine
Synevo Central Lab Ukraine
46/2 building 3
Akademik Palladin Avenue
03680 K jv. Ukraine

[redacted]

Korea/Taiwan
GCRL (Green Cross Reference Lab)
314 Bojung-dong, Giheung-gu,
Y [redacted] K [redacted] d K ea

16. REFERENCES

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17. APPENDICES

17.1. Study Organization

17.1.1. Data and Safety Monitoring Board (DSMB)

There will be an independent DSMB to protect the rights, safety and well-being of subjects participating in the study. The DSMB consists of qualified scientists who are not Investigators in the study and not otherwise directly associated with the sponsor, and has the primary role in examining the safety data and other pertinent data. The DSMB monitors study data in an un-blinded, ongoing manner and alerts 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. The DSMB can recommend modification of the study protocol, or study, or treatment regimen to the Executive Committee based on pre-specified rules described in the DSMB charter.

All activities of the DSMB will be documented. This documentation will include data summaries and analyses (see Section 11.8) provided to the DSMB as well as minutes of the meetings. 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.

17.1.2. Clinical Events Committee (CEC)

An independent CEC reviews and adjudicates the following events in a blinded manner and without any knowledge of the subject's assigned treatment regimen:

- Clinically relevant non-major bleeding;
- Major bleeding;
- Minor bleeding;
- Death from any cause;
- Suspected stroke;
- Suspected SEE;
- Suspected MI;
- Suspected stent thrombosis;

Details about the definitions of the endpoints (Section 7.3), endpoint sub-categories and other CEC processes are described in the CEC charter.

The single components of the composite primary (and secondary endpoints mentioned above are explored, as well as specific subcategories (e.g., ICH,

ischernic stroke) and event classifications according to other definitions (e.g., BARC, TIMI).

17.1.3. 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 comprised of designated representatives from the Academic Research Organizations (AROs), CRO, and Sponsor.

17.1.4. 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.

17.1.5. Operations Committee

The Operations 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.

17.2. Substudies

Subjects in this study may participate in one or more substudies. Dedicated sites are invited for participation according to sites capabilities to meet specific substudies requirements and on the required number of observations. Currently, substudies are being considered involving blood sample collection for bio marker substudy (VASP protein, anti-FXa activity, whole blood clotting time (WBCT), Health Economics Outcome Research (HEOR) and possible exploratory biomarkers. The HEOR substudy may include patient reported outcome measures (PROM), healthcare resource utilization measures and other measurements of the clinical effectiveness of the study regimens.

The substudy-specific requirements and procedures will be provided as a separate protocol of this main study. Results for the substudies will be reported subsequently to those of the main study by a separate report. Any sub-study protocol will be subject of separate approval by Regulatory Authorities and IRBs/IECs.

17.3. ISTH Bleeding Criteria

Table 17.1 : ISTH Bleeding Criteria

ISTH Bleeding Criteria (15, 16)
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 on 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.

Please refer to Section 7.3 for other details on endpoint definitions.

17.4. Definition of terms

Abnormal liver function is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic der ngement (e.g., bilirubin > 2 times the ULN, in association with aspartate aminotransferase/alanine transferase/alkaline phosphatase> 3 times the upper limit of normal, and so forth).
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 :S35% (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 regard 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 poqr time in therapeutic rarige (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 oi: result in death within 24 hours of symptom onset.
TIA: TIA is defined as an abrupt onset, over minutes to hours, ofa 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.

17.5. Components of the CHA2DS2-VASc Score and HAS-BLED Score

Table 17.2: Components of the CHA2DS2-VASc Score

CHA2DS2-VASc (29, 30)	Score
Congestive heart failure	1
Hypertension	1
Age 75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Aged 65 to 74 years	1
Sex category (i.e., female sex)	1
Maximum score	10

Abbreviations: **MI:** myocardial infarction; PAD: peripheral artery disease; TIA: transient ischemic attack; TE: thrombo-emboli$m.

Table 17.3: Comoonents of the HAS-BLED Score

HAS-BLED (31, 32)	Score
Hypertension History (systolic blood pressure > 160 mmHg systolic)	I
Abnormal Renal Function (Dialysis, transplant, Cr > 2.6 mgldL or> 200 JJmoILL)	I
Abnormal Liver Function (Cirrhosis or Bilirubin >2x ULN with AST/ALT/ALP >3x ULN)	1
Previous History of Stroke	1
Prior Major Bleeding or Predisposition to Bleeding (e.g., anemia)	1
Labile lNRs (Unstable/high INRs, TTR < 60%)	1
Elderly (Age> 65 years)	I
Drug Usage (i.e., Antiplatelet agents, NSAIDs)	I
Excessive Alcohol Use (2': 8 drinks/week)	I
Maximum score	9

Abbreviations: Cr: serum creatinine; ULN: upper limit of normal; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; INR: international normalized ratio; NSAIDs: non-steroidal anti-inflammatory drugs; TTR = time in therapeutic range; ULN = upper limit of normal.

17.6. Estimation of Creatinine Clearance (CrCL) and CKD-EPI Equation for Estimating GFR on the natural Scale

Creatinine Clearance Using Cockcroft-Gault Formula (33)

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

Greatinine Glearance 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)]

The Chronic Kidney Disease Epidemiology Equation (CKD-EPI) to estimate the glomerular filtration rate (GFR)

The table is taken out of the manuscript, published in Annals of Internal medicine 2009 (39)

r.,b/> !. *The* CICO-EPI Equ uon for Est1m;i1tng GFR on *the* N.atural Scale"

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17.7. Modified Rankin Scale

Table 17.4:Modified Rankin Scale

Score(34-36)	Description
0	No symptoms at all
I	No signi fica_nt disab ility despite symptoms; abl·e to carry out all usualauhes ana achv1t1es
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

17.8. · Regional Guideline Recommendations for INR

Table 17.5: Regional Guideline Recommendations for INR

Guideline	Ref.	Target INR Range	Start VKA at INR
Europe	(1)	2.0 - 3.0	<2.5
Korea	(37)	2.0 - 3.0	<2.5
Taiwan	#	· 2.0-3.0	< 2.5
Brazil	(38)	2.0-3.0	<2.5

n Pending publication.

17.9. Schedule of Events

Table 17.6: Schedule of Events

Visit number	1			2	3	4	5	6	7	8	9	10	11	12	13	14
Period	Screening			Planned treatment												Post-treatment
Visit	**Pre-screening**	**Baseline / randomization (DAY 1)**	**Discharge**	**V**	**TA**	**V**	**TA**	**TA**	**V**	**TA**	**TA**	**V**	**TA**	**TA**	**EOT**	**Follow-up**
Visit timing	4 h - **5 d post-PCI**			**1 M**	**2M**	**3M**	**4M**	**5M**	**6M**	**7M**	**8M**	**9M**	**10M**	**11M**	**12 M**	**JM post-EOTP**
Window (days) •				±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Inclusion/Exclusion Criteria	*X*	*X*														
Check INR ≤ 2.5 (local lab results) vs. exclusion criteria [b,c]	*X*															
Demographic information	*X*															
Study informed consent[d]		*X*														
Contact IXRS for pre-declaration• and randomization[r]		*X*														
Administer OAC and antiplatelet medications [s]		*X*	*X*													
Dispense assigned OAC and antiplatelet medications[h]			*X*	*X*		*X*			*X*			*X*				
Prior medications within 30 days of randomization		*X*														
Medical history (including bleeding history)		*X*														
Local lab results;		*X*		*X (INR 011/y)*		*X (INR 011/y)*			*X (INR 011/y)*			*X (INR 011/y)*			*X (INR 011/y)*	
Physical examination		*X*														
Vital signs [i]		*X*	*X*	*X*		*X*			*X*			*X*			*X*	*X*
12-lead ECG		*X*		*X*		*X*			*X*			*X*			*X*	*X*

Visit number	1			2	3	4	5	6	7	8	9	rn	11	12	13	14
Per iod	Screening			Planned treatment												Post-tre:itment
Visit	Pre- · scree ning	Baseline/ randomi zation (DAY 1)	Discharge	V	TA	V	TA	TA	V	TA	TA	V	TA	TA	EOT	Follow-up
Visit timing	4 h- 5 d post-PC!			IM	2M	3M	4M	S M	6M	7M	SM	M	IOM	llM	12 MP	I M post-EOTq
Window (days) •				±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Index-PC! cqronary angiograms[k]		X														
Concomitant medication		X		X		X			X			X			X	X
Blood draw for central safety lab [1]		X		X		X			X			X			X	
Urine sampling (pregnancy testing) for women with childbearing potential only		X		X	X	X	X	X	X	X	X	X	X	X	X	
Review study regimen compliance & interruptions [m]			X	X	X	X	X	X	X	X	X	X	X	X	X	
AE / events reporting "		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Obtain INR and VKA dose information monthly (VKA subjects only)[0]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AE = adverse event; ALT= alanine transaminase; AST= aspartate transaminase; ALP= alkaline phosphatase; CrCL = creatinine clearance; estimated glomerular filtration rate (GFR) M = month; ECG = electrocardiogram; eCRF = electronic case report form; EOT = end- of- treatment; h = hours; ID = identification; INR = international normalized ratio; IXRS = Interactive WebNoice Response System; LD = last dose; OAC = oral anticoagulant; P C I = percutaneous coronary interver tion; TA= Te lephone assessment; TBL = total bilirubin; VKA = Vitamin K antagonist; V = On-site visit; WBC = white blood cell.

• Visit/assessments windows are provided as a guide, but visits should be scheduled taking into account the need to dispense study medications.

b INR must be 5 2.5 at screening.

[c] Check the most recent results from local laboratory tests done post-index PCI against the exclusion criteria (estimated CrCL, hemoglobin, platelet count and WBC with differential if elevated). CrCL should be calculated by the Cockcroft-Gault formula as described in Appendix 17.6.

[d] S ubjects 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.

[e] Pre-declaration of duration of ASA treatment if randomized to VKA and of P2Y12 antagonist other than clopidogrel, if applicable.

[f] For subjects randomized to edoxaban: If subject is on: (a) VKA, the first dose ofedoxaban can be started when INR :S 2.5. (b) NOAC, discontinue OAC and start edoxaban at the time of the next scheduled NOAC dose.
Continue clopidogrel bisulfate 75 mg once-daily (or other P2Y12 antagonist) with medication as provided by IXRS and discontinue ASA, if being taken.
For subjects randomized to VKA: If subject is on: (a) VKA, continue with medication as provided by IXRS when INR :S2.5. (b) NOAC, discontinue the NOAC and start VKA at the time of the next scheduled NOAC dose.
Continue clopidogrel bisulfate 75 mg once-daily (or other P2Y12 antagonist) with medication as provided by lXRS.
Start or continue ASA (100 mg once-daily), guided by the clinical presentation (ACS or stable coronary disease) and upon the CHA2DS 2- VASc and HAS-BLED score and pre-declare use and treatment duration.

[g,h] Sponsor supplies study subjects with edoxaban, VKA, P2Y12 antagonist and ASA (if applicable) according to assigned regimen at randomization. Medication kits are assigned through the IXRS. Accountability for medications provided by DS is performed at dispensing visits and the EOT visit.
Check the most recent results from local laboratory tests done Cardiac enzymes before and after index PCI (closest to post-index PCI and most recent prior to randomization, respectively); Hemoglobin, platelet count, WBC (with differential if elevated), total bilirubin (if elevated, determine conjugated/unconjugated bilirubin fraction) done post-index PCI; Total cholesterol and triglycerides done the closest to the index-PC! procedure.
At each on-site visit, check the CrCL as estimated by the Cockcroft-Gault formula.

[j] Vital signs include sitting blood pressure, weight and height. Height only needs to be recorded at screening.

[k] In index angiograms both the right coronary artery (RCA) and left coronary artery (LCA, incl. LAD and LCX) must be imaged..

[l] Blood draw for central laboratory analysis including safety lab (lNR, liver:function, serum chemistry, hematology) as described in section 9.6. At each visit individual blood samples are collected; stored and shipped according to the Laboratory-Ma nual.

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

[n] AEs, endpoint events, and events of special interest should be reported as soon as site personnel learn of the event. Endpoint event and AE reporting jsho uld occur throughout the study and not be restricted to specific visits. If ALT or ALT>3xUNL with simultaneous TBL> 2xUNL is observed, then ALP should be determined.
Report ongoing all endpoints and all AEs including abnormal laboratory findings. Any laboratory measurements performed during unscheduled visits are collected.

[o] VKA subjects only; INR values and VKA dose are collected monthly and entered into the eCRF either during the on-site visits by local laboratory determination or during the subject's telephone assessments. INR values and VKA doses collected through the general practitioner or local anticoagulation clinic must also be pc nsidered and collected but this does not constitute a waiver for subjects planned TA or lNR determination during on-site visits.

[p] Subjects are transi ioned_to an available marketed OAC of the Invest!g tor' choice. Th Io estigator wi l_follow the transition strategy in_the app o d product label. Subjects who prematurely d1scontmue study OAC are requested to contmue chmcal follow-up w.1th either study v1s1ts or telephone contacts accordmg to this schedule.

q All randomized subjects who are on study medication (study edoxaban or VKA) at 365 days, wiJI have a post-treatment contact at 30-37 days after the EQT visit to collect data on concomitant medications, SAEs, and other safe events of interest.