Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-24. DOI: 10.1056/NEJMoa1711948

Supplementary Appendix (04 Oct 2017)

Hokusai VTE Cancer Clinical Trial (DU176b-D-U311)

ClinicalTrials.gov registration NCT02073682

This supplement contains the following items:

1. Original Protocol (v1.0, 15 Dec 2014)
2. Final Protocol (v3.0, 20 Jan 2016)
3. Summary of Protocol Changes
4. Original Statistical Analysis Plan (v1.0, 29 Feb 2016)
5. Final Statistical Analysis Plan (v 3.0, 02 Oct 2017)
6. Summary of Statistical Analysis Plan Changes

CLINICAL STUDY PROTOCOL

A PHASE 3B, PROSPECTIVE, RANDOMIZED, OPEN-LABEL, BLIND EVALUATOR (PROBE) STUDY EVALUATING THE EFFICACY AND SAFETY OF (LMW) HEPARIN/EDOXABAN VERSUS DALTEPARIN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

DU176b-D-U311

IND/EUDRACT NUMBER 63,266/2014-004708-30

VERSION 1.0, 15 DEC 2014

DAIICHI SANKYO PHARMA DEVELOPMENT

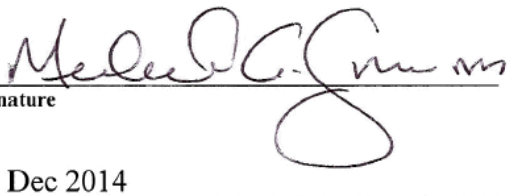
399 THORNALL STREET
EDISON, NJ 08837

INVESTIGATOR AGREEMENT

EDOXABAN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

Sponsor Approval:

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

Michael Grosso, MD	
Print Name	**Signature**
Executive Director, Clinical Development (Cardiovascular)	15 Dec 2014
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

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

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

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

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

PROTOCOL SYNOPSIS

EudraCT/IND Number:	2014-004708-30/63,266
Protocol Number:	DU176b-D-U311
Investigational Product:	Edoxaban (DU-176b)
Active Ingredient(s)/INN:	*N*-(5-Chloropyridin-2-yl)-*N*□-[(1*S*,2*R*,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
Study Title:	A Phase 3b, prospective, randomized, open-label, blind evaluator (PROBE) study evaluating the efficacy and safety of (LMW) heparin/edoxaban versus dalteparin in venous thromboembolism associated with cancer
Short Title:	Edoxaban in Venous Thromboembolism Associated with Cancer (Hokusai VTE Cancer)
Study Phase:	Phase 3b trial
Indication Under Investigation:	Venous thromboembolism associated with cancer
Study Objectives:	Primary Objectives: The primary objective is to demonstrate the non-inferiority of a 12-month course of low molecular weight heparin (LMWH)/edoxaban compared with dalteparin for the prevention of the combined outcome of recurrent venous thromboembolism (VTE) or major bleeding in subjects with VTE associated with cancer. If non-inferiority is established, edoxaban will be compared with dalteparin for superiority. Secondary Objectives: To compare LMWH/edoxaban with dalteparin with regards to rates of: 1. Recurrent VTE; 2. Major bleeding; 3. Clinically relevant non-major (CRNM) bleeding; 4. Major + CRNM bleeding; 5. Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major

	bleeding events, and death; 6. VTE-related death; 7. Mortality from all causes; 8. Recurrent deep vein thrombosis (DVT); 9. Recurrent pulmonary embolism (PE); 10. Healthcare resource utilization for potential recurrent VTE and bleed events. Exploratory Objectives: To compare LMWH/edoxaban with dalteparin with regards to: 1. Cardiovascular events (myocardial infarction [MI], stroke, systemic embolic events [SEE; see Appendix 17.5.1]); 2. Thrombotic events at other locations (see Appendix 17.5.2) 3. Reason for permanent early discontinuation of study drug.
Study Design:	This is a multinational, prospective, randomized, open-label, blind-evaluator (PROBE), non-inferiority study comparing edoxaban with dalteparin for prevention of the combined outcome of recurrent VTE or major bleeding in patients with VTE associated with cancer. One thousand subjects (1000) will be equally randomized to 1 of the 2 treatment groups. After a subject's eligibility is confirmed, the subject will be stratified by 1) bleeding risk, and 2) the need for dose adjustment, and then randomly assigned via interactive voice/web response system (IXRS) in a 1:1 ratio to treatment with either LMWH/edoxaban or dalteparin (see details in Section 3.1.2. **LMWH/Edoxaban group**: Therapeutic doses of LMWH (subcutaneous [SC]) will be administered for at least 5 days; this 5 day period may include the pre-randomization LMWH (if applicable). The choice of this parenteral LMWH is up to the treating physician. Thereafter, edoxaban will be started orally at 60 mg once daily [QD] (2 × 30 mg tablets) (30 mg QD for subjects requiring dose adjustment) for the remainder of the treatment period. **Dalteparin group**: After randomization, dalteparin will be administered at a dose of 200 IU/kg SC (maximum daily dose 18,000 IU) for 30 days. The 30 day period may

	include the pre-randomization anticoagulant treatment if dalteparin was used in therapeutic doses. Thereafter (approximately Day 31 forward), dalteparin will be administered at a dose of 150 IU/kg SC (~ 75% - 83% of the initial dose) for the remainder of the treatment period. The intended treatment duration and follow-up for all subjects is 12 months, except for the final subject(s) randomized to the study. Once 1000 subjects are randomized, a global End-of-Treatment (EOT) date will be established that ensures a minimum of 6 months of study treatment and follow-up for the final subject(s) randomized. All subjects will permanently discontinue study treatment on or before the EOT date. After randomization subjects will be assessed at Month 1, Month 3, and quarterly thereafter for up to 12 months until they complete the study. Subjects requiring additional anti-coagulation therapy who complete their treatment and full 12-month post randomization follow-up or whose treatment is truncated due to the global End of Treatment date will be managed according to local practice. Guidance for switching from edoxaban to other anticoagulants is provided in Appendix 17.2. Additional guidance for long-term management of cancer subjects with VTE is provided by Lyman, et al.[1]
Study Duration:	The expected study duration is approximately 30 months from the time the first subject is enrolled (planned for March 2015) to the time of the last subject's last follow-up visit (expected September 2017).
Study Sites and Location:	Approximately 130 study sites in North America, Europe, and Australia/New Zealand are planned to enroll subjects in this study.
Planned Sample Size:	Assuming a hazard ratio of 1, a total of 191 overall primary events is projected to accrue in the modified intention-to-treat (mITT) analysis set which will ensure at least 80% power for the primary analysis at a non- inferiority margin for the hazard ratio of 1.5 and a Type I error of 0.05 (two-sided). Assuming a primary combined outcome rate (recurrent VTE or major bleed) of 20.0%, a total of 1000 subjects are

	expected to be randomized to study treatment in order to accrue 191 overall primary events in the mITT analysis.
Subject Eligibility Criteria:	Adult male or female subjects who present with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin) for whom long-term treatment with LMWH is indicated, are eligible to participate in this study. Key eligibility criteria include: <u>Inclusion Criteria:</u> 1. Male or female subjects with age ≥ 18 years or the otherwise legal lower age according to the country of residence; 2. Confirmed symptomatic or unsuspected lower extremity proximal DVT (ie, popliteal, femoral, iliac or inferior vena cava vein thrombosis), or confirmed symptomatic PE, or unsuspected PE of a segmental or larger pulmonary artery; 3. Cancer, other than basal-cell or squamous-cell carcinoma of the skin. Cancer should be active (see Section 6.1) or diagnosed within 2 years prior to randomization. The diagnosis/history of cancer must be objectively documented; 4. Intention for long-term treatment (at least 6 months) with parenteral LMWH; 5. Able to provide written informed consent. <u>Exclusion Criteria:</u> 1. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of DVT and/or PE; 2. More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, unfractionated heparin, and fondaparinux per local labeling), oral direct anticoagulants or vitamin K antagonist (VKA) prior to randomization to treat the current (index) episode; 3. Treatment with therapeutic doses of an anticoagulant other than that used for pre-treatment of the current (index) VTE episode prior to

randomization;

4. Active bleeding or any contraindication for treatment with LMWH/dalteparin or edoxaban;
5. Indication for dalteparin other than DVT and/or PE;
6. An Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or 4 at the time of randomization (see Appendix 17.6);
7. Calculated creatinine clearance (CrCL) < 30 mL/min;
8. History of heparin associated thrombocytopenia;
9. Acute hepatitis, chronic active hepatitis, liver cirrhosis;
10. Hepatocellular injury with concurrent transaminase (alanine transaminase [ALT]/aspartate transaminase [AST] > 3 x upper limit of normal [ULN]) and bilirubin (> 2 x ULN) elevations in the absence of a clinical explanation;
11. Life expectancy < 3 months;
12. Platelet count < 50,000/mL;
13. Uncontrolled hypertension as judged by the Investigator (eg, systolic blood pressure > 170 mmHg or diastolic blood pressure > 100 mmHg despite antihypertensive treatment);
14. Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding;
15. Chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors for ≥ 4 days/week anticipated to continue during the study;
16. Treatment with aspirin in a dosage of more than 100 mg/per day or dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or intravenous antiplatelet drug) anticipated to continue during the study;
17. Treatment with the P-gp inhibitors ritonavir,

	nelfinavir, indinavir, or saquinavir anticipated to continue during the study; 18. Systemic use of the P-gp inhibitors ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin at the time of randomization; subsequent use is permitted; 19. Subjects with any condition that as judged by the Investigator would place the subject at increased risk of harm if he/she participated in the study.
Dosage Form, Dose and Route of Administration:	Edoxaban (30 mg) will be supplied by the Sponsor as yellow film-coated tablets and administered per oral (PO). LMWH for the edoxaban lead-in will be as prescribed by the Principal Investigator (see Study Design, above). Dalteparin will be supplied by the Sponsor as single-use pre-filled syringes and administered by SC injection.
Study Outcomes:	The primary study outcome is the composite of recurrent VTE, and major bleeding. <u>Recurrent VTE is either</u>: • symptomatic confirmed (new) DVT or (new) PE; • unsuspected (new) proximal DVT of the legs or unsuspected (new) PE located in segmental or more proximal arteries: – Unsuspected DVT or PE are thrombi that are detected during imaging testing performed for other reasons (eg, computed tomography (CT) for cancer staging) and not for suspicion of DVT or PE. • fatal PE (including unexplained death for which PE cannot be ruled out). <u>Secondary Outcomes</u>: • Recurrent VTE; • Major bleeding; • CRNM bleeding; • Major + CRNM bleeding; • Event-free survival, defined as the proportion of

subjects over time free of recurrent VTE, major bleeding events, and death;

- VTE-related death;
- Mortality from all causes;
- Recurrent DVT;
- Recurrent PE;
- Healthcare resource utilization for potential recurrent VTE and bleed events.

Other outcomes include:

- Cardiovascular events (MI, stroke, SEE [see Appendix 17.5.1]);
- Thrombotic events at other locations (see Appendix 17.5.2);
- Reason for permanent early discontinuation of study drug.

Statistical Analyses:

Analysis of the Primary Study Outcome

The primary analysis will be based on the mITT Analysis Set (which includes all randomized subjects who receive at least 1 dose of study drug) using all primary outcome events (ie, recurrent VTE or major bleeding) occurring from randomization through the end of the 12 month study period or up to the global EOT visit when the study has been stopped, regardless of whether the subject is taking study drug. In this analysis, the time to the first event of the composite outcome will be analyzed using a Cox's proportional hazards model including treatment and the stratification factors as covariates. The LMWH/edoxaban to comparator hazard ratio will be computed along with a 95% confidence interval [CI] (two-sided) based on this model. The LMWH/edoxaban will be considered non-inferior to the comparator if the upper limit of the CI is < 1.5.

The following sensitivity analyses will be performed for the Primary Outcome:

- On-Treatment events based on the per-protocol (PP) Analysis Set will be analyzed using the counting process approach of the Cox proportional hazards regression model including treatment group, and the stratification factors as

covariates. An On-Treatment event is defined as the event occurring during the time period the subject is taking study drug up to 3 days after their last dose for that time period. Only events occurring prior to or on Day 365 will be included into this analysis. Subjects who do not experience an On-Treatment event will be censored at Day 365, or the time study drug is permanently discontinued plus 3 days or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global end of treatment, whichever comes first.

- Events occurring during the first 6 months (180 days) based on the mITT Analysis Set will be analyzed using the same statistical model as the primary analysis of the primary outcome. The time to event is defined as the time (days) from the randomization to the first event during the first 6 months after randomization. Subjects who do not experience an event until Day 180 will be censored at Day 180, or the time study drug is permanently discontinued or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, whichever comes first.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phoshatase
ALT	Alanine transaminase
ANA	Antinuclear antibody
ARO	Academic Research Organization
AST	Aspartate transaminase
BP	Blood pressure
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence interval
CMV	Cytomegalovirus
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CrCL	Creatinine clearance
CRF	Case Report Form
CRNM	Clinically relevant non-major
CRO	Contract Research Organization
CT	Computerized tomography
CTPA	Computerized tomographic pulmonary angiography
CUS	Compression ultrasonography
CVC	Central venous cathether
DMC	Data Monitoring Committee
DTE	Data-driven Trial Execution
DOAC	Direct oral anticoagulant
DTE	Data-driven Trial Execution
DU-176b	Edoxaban tosylate
DVT	Deep vein thrombosis
EBV	Epstein Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
EIU	Exposure In Utero
EOT	End of trial
EU	European Union
FDA	Food and Drug Administration
FXa	Factor Xa
GCP	Good Clinical Practice (refers to ICH and CFR)
GI	Gastrointestinal

Abbreviation	Definition
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITREAS	International Trial Expertise Advisory and Services
IV	Intravenous
IVC	Inferior vena cava
IXRS	Interactive web/voice response System
LFT	Liver function test
LMWH	Low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified intention-to-treat
NSAIDs	Non-steroidal anti-inflammatory drugs
NVAF	Non-valvular atrial fibrillation
PCC	Prothrombin complex concentrate
PD	Pharmacodynamic
PE	Pulmonary embolism
PI	Principal Investigator
PK	Pharmacokinetic
PO	Per oral
PP	Per-protocol
PROBE	Prospective, randomized, open-label, blind-evaluator (study design)
QD	Once daily
QOL	Quality of life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SC	Subcutaneous
SDR	Source data review
SDV	Source data verification
SEE	Systemic embolic event
SMCC	Steering Management Coordinating Committee
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
SVT	Splanchnic vein thrombosis
TEAE	Treatment-emergent adverse events

Abbreviation	Definition
UFH	Unfractionated heparin
ULN	Upper limit of normal
US	United States
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
V/Q scan	Ventilation perfusion scan
WBC	White blood cell
WHODRUG	World Health Organization Drug Reference

1. INTRODUCTION AND BACKGROUND INFORMATION

Venous thromboembolism (VTE) is a common and clinically important disease in cancer patients and current standard treatment consists of long-term low-molecular weight heparin (LMWH).[1, 2, 3, 4] Although subcutaneous (SC) injections with LMWH are effective they are often difficult to tolerate and inconvenient for long-term use by cancer patients. Therefore, if oral medications, such as the current direct oral anticoagulants (DOACs) are effective and safe without the need for SC punctures, they are potentially an attractive alternative in this population. The Hokusai VTE study has shown that edoxaban, an oral direct Factor Xa (FXa) inhibitor, was effective and safe in the treatment of VTE.[5] In a subgroup analysis among 771 cancer patient randomized to the Hokusai VTE study, edoxaban was non-inferior in terms of efficacy and associated with a relative risk reduction of 19% in clinically relevant bleeding compared to warfarin.[6] In view of these results, a clinical study with edoxaban versus LMWH in cancer-associated VTE is proposed.

1.1. Data Summary

The efficacy and safety of edoxaban for the treatment of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), and the prevention of recurrent VTE was demonstrated in the Phase 3 Hokusai VTE study. A large pivotal Phase 3 study in non-valvular atrial fibrillation (NVAF) (ENGAGE AF-TIMI 48) has also been completed and provides important information regarding the safety of long-term edoxaban treatment. 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	Treatment Groups	Number of Subjects	Median Duration of Treatment	Primary Efficacy Endpoint	Primary Efficacy Outcome (Edoxaban vs Warfarin	Primary Safety Endpoint	Primary Safety Outcome (Edoxaban vs Warfarin)
Hokusai VTE (acute VTE)	Edoxaban 60 mg	4118	0.7 years	Recurrent VTE	HR (95% CI) 0.89 (0.703, 1.128)	Major + CRNM Bleeding	HR (95% CI) 0.81 (0.705, 0.936)
	Warfarin	4122					
ENGAGE AF-TIMI 48 (NVAF)	Edoxaban 60 mg	7012	2.5 years	Stroke and SEE	HR (95% CI) 0.79 (0.63, 0.99)	Major Bleeding	HR (95% CI) 0.80 (0.71, 0.91)
	Edoxaban 30 mg	7002					
	Warfarin	7012					

VTE – venous thromboembolism; HR – Hazard Ratio; CI – confidence interval; CRNM – clinically relevant non-major; NVAF – non-valvular atrial fibrillation; SEE – systemic embolic event

Other completed studies include Phase 1 clinical pharmacology studies, Phase 2 dose-ranging studies in subjects with NVAF and subjects undergoing lower-extremity orthopedic surgery, and Phase 3 studies in subjects undergoing lower-extremity orthopedic surgery. In the edoxaban program, a combined total of 18,132 subjects were treated with edoxaban (7002 with edoxaban 30 mg and 11,130 with edoxaban 60 mg) encompassing over a total exposure of > 34,048 subjects years for edoxaban.[7]

1.1.1. Investigational Product(s)

1.1.1.1. Name

Name of Investigational Product: Edoxaban tosylate (DU-176b)

Edoxaban (INN), anhydrous free base (DU-176)

Active Ingredient: *N*-(5-Chloropyridin-2-yl)-*N*□-[(1*S*,2*R*,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

1.1.1.2. Description

Edoxaban tosylate is an antithrombotic agent, an orally active, selective, direct, and reversible inhibitor of 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. Nonclinical Studies

In nonclinical studies, edoxaban showed excellent potential as an antithrombotic agent. Nonclinical data indicate no evidence of liver function abnormalities in study animals exposed to edoxaban. Additional details are available in edoxaban Investigators' Brochure.[7]

1.1.1.4. Clinical Experience

The global clinical experience with edoxaban includes 43 completed Phase 1 studies, 12 completed Phase 2 studies and 8 completed Phase 3 studies.

Edoxaban has been evaluated in the treatment of VTE in a large pivotal Phase 3 study, the Hokusai VTE study.[5] In this study, 8292 patients were enrolled: 4921 with DVT and 3319 with PE. Patients were randomized to an initial course of LMWH followed by edoxaban or LMWH/warfarin followed by warfarin alone. The primary efficacy analysis of non-inferiority versus the current standard of care (ie, heparin overlapped with warfarin until the international normalized ratio (INR) reaches ≥ 2.0) was demonstrated with a high degree of confidence (hazard ratio [HR]: 0.89; 95% confidence interval [CI]: 0.703, 1.128; p<0.0001). The efficacy was consistent across analysis populations, individual components of the primary endpoint and subgroups of subjects including older individuals, those with renal impairment and subjects with lower body weight. For the primary safety outcome (adjudicated major/clinically relevant non-major (CRNM) bleeding, Safety Analysis Set, On-Treatment Study Period), edoxaban was superior to warfarin (HR: 0.81; 95% CI: 0.71, 0.94; p=0.0040) for a relative risk reduction of 19%. The benefit was most apparent for more serious bleeding including intracerebral hemorrhage. There was an increase in gastrointestinal (GI) bleeding, in line with other

FXa inhibitors.[8] There was also an increase in vaginal bleeding, where the majority of cases were menses-related, but few cases were serious or led to discontinuation of treatment.

It was concluded that once daily edoxaban after heparin was equally efficacious and caused significantly less bleeding compared with high-quality standard therapy with warfarin in a broad spectrum of VTE patients, including those with severe PE.

Additional details are available in the edoxaban Investigators' Brochure.[7]

1.2. Study Rationale

Venous thromboembolism (comprising DVT and PE) is a serious and frequently occurring comorbidity in cancer patients. It is the second most common cause of death in these patients[9] and compared with healthy persons cancer patients have a 4- to 7-fold increased risk for developing VTE.[10, 11] The association between thrombotic disease and cancer can be explained by pathophysiological mechanisms, while chemotherapy and central venous catheters (CVCs) often used in this population further increase the risk of VTE.

In addition to a higher risk for developing VTE, patients with a malignancy when treated with anticoagulants also have an increased risk of bleeding, with major bleeding rates that are in the same range as the rate of recurrent VTE (ie, 8% - 12% per year as shown in contemporary studies).[12, 13, 14]

Given these findings, clinical studies evaluating effective and safe VTE treatment are considered a priority for cancer patients. Since the principal problem in cancer patients with VTE is the underlying cancer, VTE management should preferably not interfere with the cancer therapy and have minimal impact on the patient's already compromised quality of life (QOL). In this respect, VTE treatment in cancer patients is more challenging and different than VTE treatment in non-cancer patients. Current standard therapy for cancer-associated VTE is daily SC injected LMWH-dalteparin for at least 6 months.[1, 2, 3, 4] Although SC injections are effective they are often difficult to tolerate and inconvenient for long-term use by cancer patients. Therefore, if oral medications such as the current direct oral anticoagulants are effective and safe without the need for SC punctures then they are potentially an attractive alternative for patients with cancer and VTE. The Hokusai VTE study has shown that edoxaban, an oral direct FXa inhibitor (DOAC), was effective and safe in treatment of venous thromboembolism.[5] Additionally, among 771 patients with cancer randomized in the study, the recurrence rate over the 12-month study period in the edoxaban group was 3.7% compared with 7.1% in the warfarin group (HR: 0.53; 95% CI: 0.28, 1.00). In these same patients, the clinically significant bleeding rates were 12.4% versus 18.8% (HR: 0.64; 95% CI: 0.45, 0.92) in the edoxaban and warfarin treatment groups, respectively.[6] Interestingly, in the subgroup of patients classified by the treating physician as having cancer active at entry in the study (n=208), the risk of VTE recurrence was 3.7% in the edoxaban group and 7.1% in the warfarin group (HR, 0.55; 95% CI, 0.16, 1.85), showing virtually identical results between patients with a history of cancer and the subset of those considered by the physician to have "active" cancer. This novel observation illustrates that the risk with respect to recurrent VTE is more the history of cancer than the more narrow definition of

cancer that is "active." This conclusion was reached also in another recent study in a subgroup of cancer patients with VTE.[15]

In view of these results, a comparative clinical study between standard treatment consisting of long-term SC LMWH-dalteparin and the new oral direct FXa inhibitor, edoxaban, is proposed.

In a clinical study evaluating new anticoagulant therapy in the cancer patient population several design aspects require consideration.

- Both recurrent VTE and major bleeding are potential life-threatening complications occurring at a comparable rate and with a significant and similar impact on the patient's clinical status. The VTE-treatment should therefore aim to prevent both recurrent VTE and major bleed and in a study evaluating a new treatment option and the 2 outcomes will need to be equally considered. Therefore, in this novel design it is proposed that the primary outcome of the study will be a combined outcome consisting of recurrent VTE and major bleeding.

- In cancer patients, VTE-symptoms often are not obvious and erroneously attributed to the cancer or its treatment. This unsuspected VTE occurs frequently[16, 17, 18] and the prognosis of these unexpected VTEs in terms of recurrent VTE and mortality are similar to those with symptomatic disease. [1,19, 20, 21, 22] As a consequence, current guidelines advise a similar treatment strategy for unsuspected PE and DVT as for clinically apparent VTE.[1] Therefore, unsuspected PE and DVT will be considered as an inclusion criterion and also as a component of the primary outcome.

- In non-cancer patients the duration of VTE-treatment is at least 3 months and prolonged up to 12 months or indefinitely depending on the clinical judgment balancing risk and benefit. In cancer patients the recommended treatment duration is at least 6 months. Consistent with guideline recommendations prolonging treatment needs to be strongly considered especially in patients in whom cancer is still present.[1 ,2 ,3] However, after 6 months physicians are faced with a dilemma since data from studies beyond 6 months are absent.[1, 2, 3] In evaluating a new anticoagulant treatment it is desirable to document the effects of treatment over a longer period of time. Therefore, the intent in the present study is to treat all subjects for 12 months, and to follow all subjects for 12 months after randomization whether or not they complete 12 months of treatment. This is important because bleeding, including CRNM bleeding events, may lead to discontinuation or interruption of anticoagulant therapy, which then increases the risk of subsequent recurrent VTE events, with such events not captured using traditional On-Treatment analyses.

1.3. Risks and Benefits for Study Subjects

Edoxaban is a selective FXa inhibitor with rapid onset of action and predictable antithrombotic properties. Edoxaban appears to be well tolerated up to a dose of 90 mg QD, with expected transient and manageable bleeding adverse events (AEs) and transient and reversible liver enzyme and bilirubin elevations.

In the edoxaban program, a combined total of 18,132 subjects were treated with edoxaban (7002 with edoxaban 30 mg and 11,130 with edoxaban 60 mg) encompassing

over a total exposure of > 34,048 subjects years for edoxaban.[7] This exceptionally large database allowed the overall safety of edoxaban to be adequately characterized in terms of adverse reactions with rare frequency and those occurring after a long latency period. The program also conducted a large number of specific studies to allow characterization of the pharmacokinetic (PK) and safety profile of edoxaban in subjects with hepatic dysfunction, severe renal impairment, and concomitant medications. These specific studies together with the large clinical database allowed for the safety of edoxaban to be assessed in a large number of subject subgroups of intrinsic and extrinsic factors. Edoxaban demonstrated a consistent safety profile across subgroups. An effective oral and parenteral transition scheme from edoxaban to other anticoagulants has also been demonstrated.

The completed Phase 3 clinical trials in AF and VTE have demonstrated efficacy and safety of edoxaban 60-mg dose (with a 30-mg dose reduction in subjects with 1 or more of the following: moderate to severe renal impairment, weight ≤ 60 kg, or concomitant use of specified P-gp inhibitors) in the prevention of stroke and systemic embolism in adult subjects with NVAF and in the treatment of VTE including DVT and PE, and prevention of recurrent VTE.

For VTE in particular, the primary efficacy analysis of non-inferiority versus the current standard of care (ie, heparin overlapped to warfarin until the INR reaches ≥2.0) was demonstrated with a high degree of confidence. In the primary efficacy modified intention-to-treat (mITT) overall analysis, the edoxaban regimen demonstrated non-inferiority versus warfarin (HR: 0.89; 95% CI: 0.703, 1.128; p<0.0001). The efficacy was consistent across analysis populations, individual components of the primary endpoints and subgroups of subjects including older individuals, those with renal impairment, and lighter subjects.

Edoxaban 60 mg showed a clear benefit in terms of reduced bleeding when compared with well-controlled warfarin treatment. In the Hokusai VTE study, the primary safety endpoint (adjudicated major/CRNM bleeding, Safety Analysis Set, On-Treatment Study Period), edoxaban was superior to warfarin (HR: 0.81; 95% CI: 0.71, 0.94; p=0.0040) for a relative risk reduction of 19%. The benefit was most apparent for more serious bleeding including ICH, and intra-articular and intra-ocular bleeds. There was an edoxaban associated increase in GI bleeding, in line with other FXa inhibitors. There was also an increase in vaginal bleeding, where the majority of cases were menses-related, but few cases were serious or led to discontinuation of treatment.

Bringing together quantitatively the benefits and risks as a net clinical outcome, Table 1.2 summarizes the benefit-risk outcomes. For each indication, the net clinical outcome covers the principal efficacy and safety outcomes, and includes all-cause mortality.

Table 1.2: Quantitative Benefit Risk

Composite Endpoint	HR (95% CI) for Edoxaban 60 mg versus Warfarin
NVAF: Net Clinical Outcome mITT, Overall	0.89 (0.83 to 0.96)
VTE: Net Clinical Outcome PP, On-Treatment	0.87 (0.70 to 1.10)
HR – Hazard Ratio; CI – confidence interval; NVAF – non-valvular atrial fibrillation; mITT – modified intention-to-treat; VTE – venous thromboembolism; PP – per protocol For NVAF, net clinical outcome is a composite of stroke, systemic embolic event, major bleeding, and all-cause mortality. For VTE, net clinical outcome is a composite of symptomatic recurrent deep vein thrombosis, non-fatal symptomatic recurrent pulmonary embolism, fatal pulmonary embolism, and major bleeding, and all-cause mortality.	

Overall, edoxaban has an adequately characterized positive benefit-risk ratio in large and representative populations globally in patients with NVAF and VTE, demonstrating efficacy in the overall populations and subgroups (with dose reduction as required) in conjunction with a favorable bleed profile as well as demonstrating its effectiveness in a dose-dependent manner for VTE prevention after orthopedic surgery such as hip or knee replacement. Additional advantages of edoxaban are its once daily (QD) dosing, dose-reduction strategies to minimize the risk of bleeding with preserved efficacy and no necessity for constant monitoring of therapy.

Dalteparin is the only licensed anticoagulant for the extended treatment and prevention of recurrence of VTE in cancer patients and thus is considered the "gold" standard treatment. Six months of dalteparin was found to be more effective than, and as safe as, vitamin K antagonists [VKAs] (ie, warfarin/coumarin) for patients with cancer and acute VTE, without significantly increasing the risk of major bleeding. The authors concluded that "longer term" dalteparin is safe in cancer patients.[23]

References and information on dalteparin (Fragmin®) is available in the Summary of product Characteristics/Product Monograph and the package inserts.[24]

Complete prescribing information for dalteparin can be found in Appendix 17.1.1.

1.4. Population, Route, Dosage, Dosage Regimen, Treatment Period

Adult subjects who present with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin) for whom long-term treatment with LMWH is intended are eligible to participate in this study. Section 4 lists all eligibility requirements necessary to qualify for the study.

Eligible subjects will be stratified by 1) bleeding risk, and 2) the need for dose adjustment, and then randomized to receive either LMWH/edoxaban or dalteparin (see full details below; Section 3 provides complete treatment details).

- Edoxaban group: Therapeutic doses of LMWH (SC) for at least 5 days will be administered; this 5 day period may include the pre-randomization LMWH treatment (if applicable). The choice of parenteral LMWH is up to the treating physician. Thereafter, edoxaban will be started orally at 60 mg QD (2

× 30 mg tablets; 30 mg QD for subjects requiring dose adjustment) for the remainder of the treatment period.

- Dalteparin group: After randomization, dalteparin will be administered at a dose of 200 IU/kg SC (maximum daily dose 18,000 IU) for 30 days. The 30 day period may include the pre-randomization anticoagulant treatment if dalteparin was used in therapeutic doses. Thereafter (approximately Day 31 forward), dalteparin will be administered at a dose of 150 IU/kg SC (~ 75% - 83% of the initial dose) for the remainder of the treatment period.

1.5. 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 Conference on Harmonisation (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) and/or
- European Commission Directive (2005/28/EC Apr 2005) and/or
- Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, Parts 11, 50, 54, 56 and 312 as appropriate and/or
- Other applicable local regulations.

1.5.1. Subject Confidentiality

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

For European Union (EU) sites, 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/electronic CRF [eCRF]) or other documents submitted to the Sponsor and/or its designated representatives, subjects should be identified by a unique subject identifier as designated by the sponsor. Documents that are not for submission to Sponsor and/or it's designated representatives (eg, signed Informed Consent Forms [ICFs]) should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/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) or Institutional Review Board (IRB) direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

1.5.2. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject or legally acceptable representative 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 (see Section 6.1 Study Qualification). A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The written ICF should be prepared in the local language(s) of the potential subject population.

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

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the subject or a legally acceptable representative, and by the appropriate qualified person who conducted the informed consent discussion (not necessarily the Investigator but delegated by the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legal representative. The date that informed consent was given should be recorded on the CRF.

If the subject or legally acceptable representative cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject or the legally acceptable representative has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject or the legally acceptable representative.

Suggested model text for the ICF for the study and any applicable subparts (genomic, pharmacokinetic, etc) are provided in the Sponsor ICF template for the Investigator to prepare the documents to be used at his or her site. Updates to applicable forms will be communicated via letter from the Clinical Study Manager.

This study will be conducted in the United States (US), therefore, additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

1.5.3. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator brochure, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about

payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the IEC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the Statistical Analysis Plan (SAP).

The Investigator must submit and, where necessary, obtain approval from the IEC or IRB and/or Sponsor for all subsequent protocol amendments and changes to the informed consent document or changes of the site, facilities or personnel. The Investigator should notify the IEC or IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Sponsor/contract research organization (CRO), in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will ensure 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 Objective

The primary objective is to demonstrate the non-inferiority of a 12-month course of LMWH/edoxaban compared with dalteparin for the prevention of the combined outcome of recurrent VTE or major bleeding in subjects with VTE associated with cancer. If non-inferiority is established, edoxaban will be compared with dalteparin for superiority.

2.1.2. Secondary Objectives

The secondary objectives are to compare LMWH/edoxaban with dalteparin with regards to rates of:

1. Recurrent VTE;
2. Major bleeding;
3. CRNM bleeding;
4. Major + CRNM bleeding;
5. Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
6. VTE-related death;
7. Mortality from all causes;
8. Recurrent DVT;
9. Recurrent PE;
10. Healthcare resource utilization for potential recurrent VTE and bleed events.

2.1.3. Exploratory Objectives

Exploratory objectives include comparing LMWH/edoxaban with dalteparin with regards to:

1. Cardiovascular events (myocardial infarction (MI), stroke, SEE [see Appendix 17.5.1]);
2. Thrombotic events at other locations (see Appendix 17.5.2);
3. Reason for permanent early discontinuation of study drug.

2.2. Study Hypothesis

Edoxaban will be non-inferior to dalteparin with respect to the occurrence of recurrent VTE or major bleeding in the treatment of VTE associated with cancer.

The study treatment (edoxaban) will be considered non-inferior to the standard therapy (dalteparin) if the upper limit of the two-sided 95% CI for the hazard ratio (edoxaban/standard therapy) is < 1.5.

3. STUDY DESIGN

3.1. Overall Plan

3.1.1. Study Type

This is a multinational, prospective, randomized, open-label, blind-evaluator (PROBE), non-inferiority study comparing edoxaban with dalteparin for prevention of the combined outcome of recurrent VTE or major bleeding in patients with VTE associated with cancer. Adult subjects with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin; cancer should be active (see Section 6.1) or diagnosed within the previous 2 years), and who present with confirmed acute symptomatic or unsuspected lower extremity proximal DVT, confirmed symptomatic PE, or unsuspected PE in a segmental or larger pulmonary artery for whom long-term treatment (at least 6 months) with LMWH is indicated are eligible to participate in this study. One thousand subjects (1000) will be equally randomized to 1 of the 2 treatment groups.

After a subject's eligibility is confirmed, the subject will be stratified by 1) bleeding risk, and 2) the need for dose adjustment, and then randomly assigned via interactive voice/web response system (IXRS) in a 1:1 ratio to treatment with either LMWH/edoxaban or dalteparin (see Section 5.1.1 for complete details).

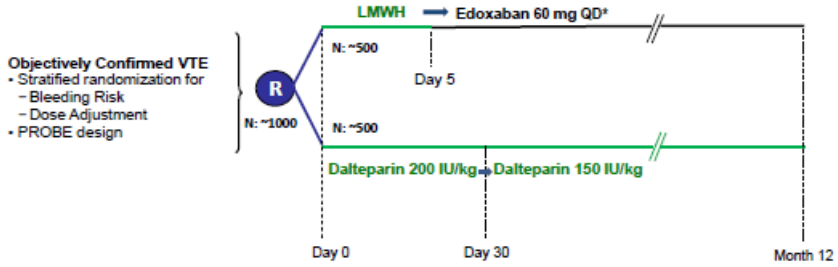
After randomization subjects will be assessed at Month 1, Month 3, and then quarterly thereafter for up to 12 months until they complete the study.

Approximately 130 study sites in North America, Europe, and Australia/New Zealand are planned to enroll subjects in this study.

3.1.2. Treatment Groups and Dosing

Figure 3.1 depicts the study design and treatment plan. The detailed Schedule of Events is provided in Appendix 17.7 and the protocol-required study procedures are provided in Section 6.

Figure 3.1: Study Design



Eligible subjects will be stratified by 1) bleeding risk, and 2) the need for dose adjustment:

1. Bleeding risk (assessed at time of randomization)
   - surgery within 2 weeks prior to randomization
   - use of antiplatelet agents (eg, aspirin ≤ 100 mg/day) that will continue during the study
   - brain tumor or brain metastases present at the time of randomization
   - metastatic disease present at the time of randomization
   - regionally advanced cancer present at the time of randomization
   - gastrointestinal cancer at randomization or diagnosed within a 6-month period prior to randomization
   - urothelial cancer at randomization or diagnosed within a 6-month period prior to randomization
   - Avastin (bevacizumab) use at randomization or given within the 6-week period prior to randomization
2. The need for dose adjustment
   - body weight ≤ 60 kg, or
   - creatinine clearance (CrCL) between 30 and 50 mL/min inclusive
   - concomitant use of P-gp inhibitors

After stratification, subjects will be assigned randomly via IXRS in a 1:1 ratio to 1 of the 2 following treatment groups:

- **LMWH/Edoxaban group**: Therapeutic doses of LMWH (SC) will be administered for at least 5 days; this 5-day period may include the pre-randomization LMWH (if applicable). The choice of this parenteral LMWH

is up to the treating physician. Thereafter, edoxaban will be started orally at 60 mg QD (2 × 30 mg tablets; 30 mg QD for subjects requiring dose adjustment) for the remainder of the treatment period.

The first dose of edoxaban should be taken:

- 12 (±3) hours after the last injection of the initial LMWH if this was a twice daily regimen,
- 24 (±3) hours after the last injection of the initial LMWH if this was a once daily regimen.

The edoxaban daily dose should be decreased to 30 mg QD for:

- body weight ≤ 60 kg; or
- creatinine clearance [CrCL] between 30 and 50 mL/min inclusive;
- concomitant use of P-gp inhibitors (eg, hormonal agents: tamoxifen, enzalutamide, abiraterone).

Dose reduction of edoxaban to 30 mg QD is intended only during concomitant use of P-gp inhibitors. When use of these inhibitors is discontinued/intermittent (eg, between chemotherapy cycles) the full 60 mg edoxaban dose should be used.

After randomization, if the subject's CrCL becomes ≤ 50 mL/min and ≥ 30 mL/min and the decrease in CrCL is > 20% from the subject's baseline CrCL value, repeat the measurement in 1 week. If the repeat measurement confirms this decrease, the edoxaban dosage regimen will be reduced permanently, even if the subject subsequently experiences improved CrCL to > 50 mL/min at a later measurement.

After randomization, if the subject's body weight drops to ≤ 60 kg (confirmed by repeat measurement at least 1 week apart) and the body weight change is > 10% of the subject's baseline body weight, the edoxaban dosage regimen will be reduced permanently, even if the subject subsequently re-gains weight to > 60 kg.

More details are provided in Appendix 17.3.7.

- **Dalteparin group**: After randomization, dalteparin will be administered at a dose of 200 IU/kg SC (maximum daily dose 18,000 IU) for 30 days. The 30 day period may include the pre-randomization anticoagulant treatment if dalteparin was used in therapeutic doses. Thereafter (approximately Day 31 forward), dalteparin will be administered at a dose of 150 IU/kg SC (~ 75% - 83% of the initial dose) for the remainder of the treatment period.

Dalteparin doses by weight and precautions for dose modifications are listed in Appendix 17.4 .

3.1.2.1. Treatment Duration

The intention is to treat patients for 12 months with the allocated study treatment.

Continuation of anticoagulant treatment beyond 6 months will be based on the risk-benefit evaluation by the treating physician.

Continue anticoagulation treatment if the benefit of doing so outweighs the risk and/or cancer is still "active". In this case ongoing anticoagulation with the allocated treatment regimen is preferred (if this is considered appropriate by the Investigator). If however the Investigator decides to switch to another treatment regimen (eg, in the dalteparin arm the decision can be made to stop the parenteral administration and switch to oral therapy), it is recommended to switch to VKA and strongly discouraged to switch to a DOAC.

Note: All subjects, including those in whom study medication is stopped or those who switch to VKA, will be followed up to 12 months with the following exception:

Once 1000 subjects are randomized in the study, a global end-of-treatment (EOT) date will be established that ensures a minimum of 6 months of study treatment and follow-up for the final subject(s) randomized. All subjects will permanently discontinue study treatment on or before the EOT date.

3.1.3. Study Governance

3.1.3.1. Steering Committees

The study oversight will be managed by a Steering Management Coordinating Committee (SMCC) whose members are country coordinators, as well as, non-voting representatives of the Sponsor and Academic Research Organization (ARO). In this study, International Trial Expertise Advisory and Services (ITREAS) will function as the ARO.

An Executive Committee to the SMCC will have a scientific advisory function and will not be involved in operational matters.

Ongoing study oversight and management will be the responsibility of a joint supervisory committee. The members of this committee are the chairman and co-chair of the SMCC and designated representatives from the Sponsor, CRO and ARO.

3.1.3.2. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will monitor safety during the study and give recommendations to the Executive Committee. The DMC will periodically review and examine the safety and efficacy data (mortality and events, bleeding events, serious adverse events [SAEs], systemic embolic event [SEE]) and alert the Chairman of the Executive Committee in case of any clinically concerning safety issues.

3.1.3.3. Clinical Events Committee

An independent Clinical Events Committee (CEC) will be established to objectively adjudicate and categorize the presenting index diagnosis, VTE outcomes, cardiovascular events, bleeding events, selected hepatic events, and death. Adjudicators will be blinded as to subject treatment allocation.

3.1.4. Study Outcomes

3.1.4.1. Primary Outcome

The primary outcome is the composite of recurrent VTE, and major bleeding.

All suspected recurrent VTE and bleeding events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

See Section 7.1 for complete details of the primary outcome.

3.1.4.2. Secondary Outcomes

Secondary outcomes include:

- Recurrent VTE;
- Major bleeding;
- CRNM bleeding;
- Major + CRNM bleeding;
- Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE -related death;
- Mortality from all causes;
- Recurrent DVT;
- Recurrent PE;
- Healthcare resource utilization for potential recurrent VTE and bleed events.

All suspected VTE events, deaths, and bleeding events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

3.1.4.3. Other Outcomes

Other outcomes include:

- Cardiovascular events (MI, stroke, SEE[see Appendix 17.5.1]);
- Thrombotic events at other locations (see Appendix 17.5.2);
- Reason for permanent early discontinuation of study drug.

All suspected cardiovascular events and other thrombotic events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

3.2. Selection of Doses

3.2.1. Experimental Treatments

In the current guidelines extended LMWH therapy is the first choice for long-term treatment of VTE in cancer patients.[1, 2, 3] Dalteparin is the only approved anticoagulant specifically indicated for the extended treatment and prevention of recurrent VTE in cancer patients; thus, it is considered the standard of care. The dalteparin regimen to be used in this study is based on the CLOT study which showed that 6 months of dalteparin was more effective than and as safe as VKAs (ie, warfarin/coumarin) for patients with cancer and acute VTE, without significantly increasing the risk of major bleeding.[23]

The edoxaban regimen (60 mg QD with dose reduction for specific risk factors) was selected for this study based on the Hokusai VTE study results. In the Hokusai VTE study, edoxaban produced a 47% relative reduction in risk for recurrent VTE in subjects with a history of cancer compared with warfarin. Additionally, edoxaban resulted in a 36% relative reduction for risk of clinically significant bleeding in these same subjects.[25]

4. STUDY POPULATION

4.1. Enrollment

Subjects must sign and date the ICF provided by the site before any study-specific qualification procedures are performed, except as noted in Section 6.1 Study Qualification/Pre-randomization.

4.1.1. Inclusion Criteria

Adult subjects presenting with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin) for whom long-term treatment with LMWH is intended are eligible to participate in the study.

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

1. Male or female subjects with age ≥ 18 years or the otherwise legal lower age according to the country of residence;
2. Confirmed symptomatic or unsuspected lower extremity proximal DVT (ie, popliteal, femoral, iliac or inferior vena cava (IVC) vein thrombosis), or confirmed symptomatic PE, or unsuspected PE of a segmental or larger pulmonary artery;
3. Cancer (other than basal-cell or squamous-cell carcinoma of the skin), either active or diagnosed within 2 years prior to randomization. [Note: Diagnosis of cancer must be objectively documented];
4. Intention for long-term treatment (at least 6 months) with parenteral LMWH;
5. Able to provide written informed consent.

4.1.2. Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for enrollment:

1. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of DVT and/or PE;
2. More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, unfractionated heparin, and fondaparinux per local labeling), oral direct anticoagulants or VKA prior to randomization to treat the current (index) episode;
3. Treatment with therapeutic doses of an anticoagulant other than that used for pre-treatment of the current (index) VTE episode prior to randomization;
4. Active bleeding or any contraindication for treatment with LMWH/dalteparin or edoxaban;
5. Indication for dalteparin other than DVT and/or PE;
6. An Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or 4 at the time of randomization (Appendix 17.6);

7. Calculated CrCL < 30 mL/min;
8. History of heparin associated thrombocytopenia;
9. Acute hepatitis, chronic active hepatitis, liver cirrhosis;
10. Hepatocelullar injury with concurrent transaminase (ALT/AST > 3 x ULN) and bilirubin (> 2 x ULN) elevations in the absence of a clinical explanation;
11. Life expectancy < 3 months;
12. Platelet count < 50,000/mL;
13. Uncontrolled hypertension as judged by the Investigator (eg, systolic blood pressure (BP) > 170 mmHg or diastolic blood pressure > 100 mmHg despite antihypertensive treatment);
14. Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding;

    Note: Childbearing potential without proper contraceptive measures (ie, a method of contraception with a failure rate < 1 % during the course of the study including the observational period). These methods of contraception according to the note for guidance on nonclinical safety studies for the conduct of human trials for pharmaceuticals (CPMP/ICH/286/95, modification) include consistent and correct use of hormone containing implants and injectables, combined oral contraceptives, hormone containing intrauterine devices, surgical sterilization, sexual abstinence, and vasectomy for the male partner).
15. Chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors for ≥ 4 days/week anticipated to continue during the study;
16. Treatment with aspirin in a dosage of more than 100 mg/per day or dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or intravenous [IV] antiplatelet drug) anticipated to continue during the study;
17. Treatment with the P-gp inhibitors ritonavir, nelfinavir, indinavir, or saquinavir anticipated to continue during the study;
18. Systemic use of the P-gp inhibitors ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin at the time of randomization; subsequent use is permitted;
19. Subjects with any condition that as judged by the Investigator would place the subject at increased risk of harm if he/she participated in the study.

4.2. Removal of Subjects From Therapy

4.2.1. Reasons for Withdrawal/Early Discontinuation

A subject may discontinue or interrupt study drug for a number of reasons including, but not limited to, those listed below:

Permanent Early Discontinuation

- Death;
- Withdraw of consent as defined in Section 4.2.1.2;
- Lost to follow-up as defined in Section 4.2.1.3 (every attempt will be made by the Investigator not to have subjects "lost to follow-up");
- CrCL decrease to < 30 mL/min, confirmed by repeat testing at least 1 week later or need for kidney dialysis;
- Investigator judgment due to:
  - SAE or other safety concern eg,
    - Major life-threatening bleeding
    - Onset clinical jaundice or other overt signs of liver toxicity
  - Unfavorable benefit-to-risk evaluation for continuing anticoagulant treatment
- Subject decision (refusal for intake or administration of study drugs). It is important to distinguish between withdrawal of consent with regards to continuing on study medication but continuing to be followed on study;
- Termination of all or part of the study by the SMCC acting in concert with the Sponsor.

4.2.1.1. Temporary Interruption

Temporary interruptions of edoxaban and dalteparin for 4 or more consecutive days will be recorded in the eCRF. Interruptions of edoxaban and dalteparin for less than 4 consecutive days will not be recorded in the eCRF. Potential reasons may include:

- Short-term use of prohibited concomitant medications;
- Surgical procedures;
- Any medical condition where continuing study drug may expose the subject to an increased hazard;
- New onset of elevated liver enzymes in the absence of a known cause:
  - ALT > 8 × ULN
  - AST or ALT > 5 x ULN for more than two weeks
  - ALT or AST > 3 x ULN, but not reaching the limits in the above criteria, in combination with clinical symptoms suggestive of hepatitis
  - ALT or AST > 3 x ULN with TBL > 2 x ULN

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

is, however, discouraged to switch to another DOAC. Guidance for switching from edoxaban to other anticoagulants is provided in Appendix 17.2.

Post-randomization changes (other than CrCL decreased to < 30 mL/min or need for kidney dialysis) in health status related to study exclusion criteria should not automatically lead to study drug interruption or discontinuation unless continuing study drug places the subject at undue hazard as determined by the Investigator. Such situations should be handled on a case-by-case basis. It is strongly recommended that the Investigator consults with ITREAS (Medical Support Line: +32 495 54 74 51) if a subject has a post randomization change in health status that is associated with an exclusion criterion.

Also, a decision to stop prematurely the overall recruitment in the study and/or intake of study drug can be taken by the Executive Committee /Sponsor following advice on safety aspects of the study by the DMC. The IECs/IRBs will be informed of this decision. The DMC stopping guidelines will be defined prior to the start of the study. The Sponsor has the right to close this study and the right to close a center, at any time, although this should occur only after consultation between involved parties and the Executive Committee. The IECs/IRBs must be informed. Should the site be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the Sponsor. The Investigator will retain all other documents until notification by Sponsor for destruction

If the subject is withdrawn due to an adverse event, the Investigator will follow the subject until the adverse event has resolved or stabilized.

4.2.1.2. Withdrawal of Consent from Study Participation

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw consent 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.

However, it is important to distinguish between withdrawal of consent with regards to continuing on study medication (but continuing to be followed on study) versus withdrawal of consent with regards to discontinuing the study all together (ie, withdrawal of consent with regards to continuing on study medication and any further study follow-up).

Only subjects who refuse all 4 of the following methods of follow-up will be considered to have withdrawn consent from study participation:

- Participation in the trial follow-up visits per protocol, either in clinic or by telephone;
- Contact by trial personnel even if only by telephone (quarterly, bi-annually, annually, End of Treatment visit only);
- Permission for trial personnel to contact an alternative person (eg, family member, spouse, partner, legal representative, physician, the anticoagulation clinic, or another healthcare provider) even if only by telephone;

- Permission for trial personnel to access and review their medical information from alternative sources (eg, doctor's notes, hospital records).

If the subject refuses all 4 of the above methods of follow-up, the Investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. If the subject continues to refuse all potential methods of follow-up, the Investigator will document this as a withdrawal of consent in the medical record.

All subjects should be followed for the full duration of the trial using any or all of the above methods, unless there is written documentation by the Investigator of the subject's withdrawal of consent to ALL of the above methods of follow-up.

If a subject is withdrawn entirely from the study, the IXRS will be called by the site to register the subject as permanently discontinued from the study (and study treatment if not done previously).

The site will complete and report the observations as thoroughly as possible up to the date of consent withdrawal and including the date of the final dose of study drug. The reason(s) for limited follow-up/data collection will be clearly documented in the medical record and eCRF.

Public databases and subject finder services may be used to determine subject status and to locate potential lost to follow-up patients.

4.2.1.3. Subjects Lost to Follow-Up

The Investigator will make every effort not to have any subjects lost to follow-up. If a subject is potentially lost to follow-up (eg, missed study visits, unable to be contacted by phone), the Investigator will make every effort to contact the subject before the subject is declared lost to follow-up. These efforts may include but are not limited to:

- Calling all telephone numbers for the subject and their contacts (including during the evening and on weekends);
- Calling primary care physician, referring specialist and/or other listed physicians for more recent locator information, date of last office visit, or to determine mortality status;
- Sending email and follow with mailing certified letters (return receipt requested) to all known subject addresses and all listed contacts (eg, relatives, friends, neighbors);
- Reviewing subject's records and medical notes for any details of a hospitalization, doctor's visit, or other procedure that may indicate status of subject;
- Using the Internet to search for possible contact information for subject
  - Try reverse directory for phone numbers to get possible addresses
  - Utilize social networking sites (eg, Facebook);

- Checking local, regional, and national public records to locate subject or search for mortality status in accordance with local law;
- Possible home visit.

Once the site has exhausted and documented these actions, the Clinical Research Associate or monitor should be contacted for additional guidance and alternative options. Public databases and subject finder services may be used to determine subject status and to locate potential lost to follow-up patients.

4.2.2. Withdrawal Procedures

4.2.2.1. Follow-Up of Subjects with Study Drug Discontinuations

The Investigator may contact ITREAS (Medical Support Line: +32 495 54 74 51) or email) in case of any questions regarding how to handle a study drug discontinuation or interruption.

All randomized subjects, including those who temporarily interrupted or discontinued study drug, will be followed for a 12-month period after randomization, except when the study is truncated as noted in Section 3.1.2.1.

In case of premature discontinuation of treatment, study outcomes can be collected by telephone contact until 12 months after the first dose of study drug. If the subject has an on-site visit at any time after study drug discontinuation, it is expected that a clinical status will be obtained along with any laboratory assessments deemed appropriate by the Investigator.

If the subject and Investigator agree that study drug can be resumed without increased hazard to the subject, study medication may be resumed at any time, regardless of the duration of study drug interruption.

Any subject who temporarily interrupts or discontinues study drug due to confirmed liver enzyme abnormalities or jaundice in the absence of a known cause, must have an evaluation to determine the cause of the event. Evaluation may include the following depending on the clinical situation:

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

Follow-up of liver enzymes and bilirubin (total and direct) should be performed on a weekly basis until the values return to baseline.

All laboratory results, including local laboratory reference ranges are to be recorded in the eCRF.

If the subject and Investigator agree that study drug can be resumed without increased

hazard to the subject, blinded study drug may be resumed at any time, regardless of the duration of study drug interruption.

All clinically significant hepatic enzyme abnormalities and/or hepatic events are to be documented in the eCRF and prompt submission of the adjudication dossier should also occur when indicated/directed (see Section 9.3.1).

5. TREATMENTS ADMINISTERED

5.1. Investigational Products

The Investigator must ensure that the investigational products will be used only in accordance with the protocol.

- Edoxaban (30 mg) will be supplied by the sponsor as yellow film-coated tablets and administered orally (PO).
- LMWH for the edoxaban lead-in will be as prescribed by the Principal Investigator (PI).
- Dalteparin will be supplied by the Sponsor as single-use pre-filled syringes and administered by SC injection.

The Investigator or designee will be responsible for dispensing study drugs.

The Investigators/study coordinators must ensure that the appropriate fields on the label are completed, including subject number and date of dispensing.

Subjects must be supplied with sufficient study drug to last until the next scheduled dispensing visit.

Subjects may take edoxaban with or with or without food, in the AM or PM, but at approximately the same time every day. Dalteparin should also be consistently administered at approximately the same time every day as well.

5.1.1. Method of Assigning Subjects to Treatments and Dispensing of Study Drug

Eligible subjects will be stratified by 1) bleeding risk, and 2) the need for dose adjustment. After confirmation of eligibility, the Investigator will provide the IXRS with the study center number, appropriate demographic information consistent with local regulations, bleeding risk profile, CrCL, body weight category (≤ 60 kg or > 60 kg), and whether the subject's currently using any P-gp inhibitors.

The IXRS will assign the unique subject identification number, stratify the subject by bleeding risk and need for dose adjustment, then allocate the treatment group assignment for the subject. A fax or email will be sent by the IXRS to the study site noting the treatment group and dosage strength of the assigned medication. The fax or e-mail will also provide a calendar of subsequent dispensing dates. Study drug will be dispensed at randomization, approximately Day 31, Month 2 then at least once every 3 months (more frequent dispensing of study drug is allowed if necessary), thereafter while the subject remains on treatment.

This study has an open-label, blind-evaluator design with LMWH/edoxaban and dalteparin. The subjects, Investigators, Sponsor, CRO, and ITREAS staff involved in the treatment or clinical evaluation of the subjects will be aware of the treatments received. There will be an independent DMC to monitor the efficacy and safety data on a periodic basis. All study outcome events will be adjudicated by the CEC using blinded evaluators.

The specifications for generation of the randomization schedule will be prepared by the study biostatistician and the CRO in charge of the IXRS. For this study, the randomization schedule refers to a list that includes the randomization number, randomization block number, and treatment.

5.1.2. Method of Assessing Treatment Compliance

Dosing compliance will be assessed by means of edoxaban tablet and dalteparin syringe counts.

5.1.3. Labeling and Packaging

Edoxaban 30 mg tablets for oral use will be supplied by the Sponsor in PVC/foil blister packs.

Dalteparin will be supplied in pre-filled syringes.

Drug labeling will be according to national law and Good Manufacturing Practice (GMP) ruling Annex 13.19.

5.1.4. Storage

5.1.4.1. Edoxaban

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

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

5.1.4.2. Dalteparin

Dalteparin must be stored at controlled room temperature below 25°C (77°F).

5.1.5. Drug Accountability

The IXRS will contain a Drug Accountability Module for any medications provided by the Sponsor (eg, edoxaban, dalteparin). The Investigator or designee will enter the required information (see IXRS user manual) in the IXRS drug accountability module. In addition, the Investigator or designee shall contact Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the investigational products. The record must be kept current and should contain, the dates and quantities of drug received, subject's (identification number and/or initials or supply number as applicable), for whom the investigational product was dispensed, the date and quantity of investigational product dispensed and remaining, if from individual subject drug units as well as the initials of the dispenser.

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

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

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

5.2. Concomitant Medications

Pre-specified medications that the subject has taken within 30 days before randomization or during the study will be recorded in the "targeted concomitant medications" eCRF. These pre-specified medications taken by the subjects upon entry to the study or at any time during the study are regarded as targeted concomitant medications and must be documented on the appropriate pages of the eCRF. If the subject has an endpoint event or an SAE, then information on targeted and non-targeted concomitant medications taken within the past 30 days must be documented on the appropriate eCRF pages. Concomitant therapy will be captured until the subjects completes the 12-month study period.

A list of specifically excluded medications is provided in Appendix 17.3. The list reflects the list at the beginning of the study. If there are changes to this list during the study, the changes will not be considered a protocol amendment but updated information. It is strongly encouraged to restrict the dose of aspirin (if indicated) to ≤ 100 mg daily, although higher doses are permitted for strong clinical indication (eg, development of an acute MI).

5.3. Therapeutic Management of Subjects in Emergency Situations

5.3.1. Bleeding

There is no specific antidote to reverse the effect of edoxaban. The following steps are recommended for subjects with ongoing life-threatening bleeding (bleeding resulting in hemodynamic compromise requiring intervention or any intracranial hemorrhage):

- Withhold study drug and all antiplatelets/anticoagulants;
- Institute standard of care for life-threatening bleeding (large bore IV or central venous line, type and crossmatch blood, admit to the intensive care unit, provide hemodynamic and respiratory support);
- Administer antidotes if applicable (eg, administer protamine if the subject had recently received heparin);

- Administer packed red blood cells (or whole blood) as needed.

If life-threatening bleeding persists, it is recommended to contact the ITREAS Medical Support Line (+32 495 54 74 51) to discuss subject management. Use of prothrombin complex concentrates (PCCs), recombinant Factor VIIa, other factor procoagulants, or antifibrinolytics (depending upon the clinical situation and local availability) should be considered in consultation with an expert and the ITREAS Medical Support Line.

5.3.2. Emergency Surgery

If an urgent surgical intervention is needed, anticoagulant therapy should be discontinued and the surgery should be deferred, if possible, until at least 12 hours and ideally 24 hours after the last administration of anticoagulant therapy. There is no reversal agent for edoxaban. Protamine can be used to (partially) reverse the effect of LMWH. Depending upon the clinical situation and local availability, the use of factor procoagulants or other measures can be considered in case of the recent intake of edoxaban prior to the surgical procedure. It is recommended to consult the ITREAS Medical Support Line (+32 495 54 74 51) in case of urgent surgery.

5.3.3. Suspected Recurrent VTE

In case of suspected recurrent VTE, the Investigator may decide to treat the subject according to the standard of care.

5.4. Therapeutic Management of Subjects for Planned Interventions

Given the half-life of both study medications and the interval of dosing (ie, once a day) it is advised to withhold the study medications at least 24 hours prior to the planned intervention. Study drug can be resumed upon complete hemostasis and after the assessment of the bleeding risk, ie, after 6 to 24 hours for most minor procedures and after 2-3 days for most surgical procedures that carry a bleeding risk. Antithrombotic therapy other than the study drug can be initiated, eg, a (prophylactic) dose of LMWH, according to the institutional best practice, until re-initiating dosing of the study drug is considered to be appropriate.

It is recommended to consult the ITREAS Medical Support Line (+32 495 54 74 51) in case of any further questions on the management of subjects who need a planned intervention.

5.5. Therapeutic Management of Subjects in Other Critical Situations

Other critical situations could be admission to hospital for acute medical illness or active periods of chemotherapy. In these circumstances gastrointestinal disorders might preclude intake of oral therapy with edoxaban and bridging to LMWH is allowed according to the guidance in Appendix 17.2. In case of doubt it is recommended to contact the ITREAS Medical Support Line (+32 495 54 74 51).

5.6. Therapeutic Management of Subjects Beyond Month 12 and at Global End-of-Treatment

Subjects requiring additional anti-coagulation therapy who complete their treatment and full 12-month post randomization follow-up or whose treatment is truncated due to the global End of Treatment date will be managed according to local practice.

Guidance for switching from edoxaban to other anticoagulants is provided in Appendix 17.2.

Additional guidance for long-term management of cancer subjects with VTE is provided by Lyman, et al.[1]

6. STUDY PROCEDURES

The Schedule of Study Procedures for this study is provided in Appendix 17.7.

6.1. Study Qualification/Pre-randomization

It is expected that most subjects will have had some or all of the study qualification procedures done as part of routine care outside the auspices of this study (for example, diagnostic work-up and associated care for VTE). If these procedures are done prior to randomization, they may be used to randomize the subject to study and begin completion of the eCRF, once the subject has signed the ICF. The subject does not need to repeat recently completed procedures/tests for study qualification. For such subjects it may be possible to combine the study qualification and randomization visits into a single visit.

Any protocol-specified study qualification procedures/tests not already done as part of routine care will be conducted only after the subject signs the ICF and before randomization. Prior to signing the ICF, potential subjects will have the study risks and benefits explained to them, the associated ICF will be reviewed, and all questions answered for them.

The following study qualification procedures must be completed to ensure that the subject is eligible for the study.

- Sign ICF;
- Review inclusion/exclusion criteria, and ensure that the subject qualifies with regard to the clinical laboratory tests for exclusion criteria:
  - Calculated CrCL < 30 mL/min;
  - Platelet count < 50,000/mL
- Review concomitant medications for assessment of exclusion criteria;
- Ensure that the subject has a diagnosis of VTE confirmed by appropriate imaging methods;

The following imaging methods are typically considered part of routine hospital work-up for the management of VTE and/or cancer, and as such, will normally be obtained prior to informed consent as part of the subject's normal standard-of-care.

- For a suspected symptomatic DVT: compression ultrasonography (CUS), venography, or specific computerized tomography (CT) venography.
- For unsuspected DVT: a thrombus detected in the IVC or iliac veins on a (staging) abdominal or pelvic CT will be considered diagnostic. Because of potential flow artifacts and layering of contrast, a suspected thrombus detected in the common femoral vein or more distal can only be considered if confirmatory CUS or (CT) contrast venography diagnostic criteria are also met.

- For suspected symptomatic PE: Computerized tomographic pulmonary angiography (CTPA; also called spiral CT angiography [spiral CT]), ventilation perfusion scan (V/Q scan; if perfusion scan only is done a confirmatory test for leg DVT is required), or catheter pulmonary angiography.

Note: A perfusion scan (without ventilation scan) does not qualify for the diagnoses of PE, unless concomitant DVT is documented.

- For an unsuspected PE: found during a staging-CT a repeat test is not recommended in order to limit radiation and contrast exposure. This incidental finding will only be considered diagnostic if the clot is in a segmental or greater artery, whereas clots in sub-segmental or more peripheral arteries will not be accepted due to risk of a false positive result.

- Record demographic information;
- Record medical/surgical history, including co-morbidities;
- Record description of cancer (date of diagnosis, type, (ie, histologically or cytologically diagnosed solid tumor), location or hematological malignancy, stage (eg, early, regionally advanced, metastatic), details on therapeutic management);
- Based on data completed in the eCRF it will be assessed whether subject meets the criteria for active cancer which will be defined as:
  - Diagnosed with cancer within the past 6 months; or
  - Recurrent, regionally advanced or metastatic disease;
  - Currently receiving treatment or have received any treatment for cancer during the 6 months prior to randomization; or
  - A hematologic malignancy not in complete remission

Note: Subjects not meeting these criteria will be categorized as history of cancer and then cancer should have been diagnosed within the 2 years preceding randomization.

- Perform physical examination including vital signs (sitting BP and heart rate) and record height and body weight (may be performed by an Investigator or other healthcare provider designated by the Investigator);
- Assess the subject for active bleeding, high risk for bleeding, and any other contraindications for treatment with LMWH or edoxaban.

Samples obtained as part of routine care outside study auspices may be analyzed by local laboratories and the results used to qualify the subject provided the tests were performed within 72 hours of randomization.

Full documentation for the above study qualification procedures and related results are required, including local laboratory results used to qualify the subject. Therefore, the eCRF must be completed for every subject with a signed ICF.

An index event dossier must be compiled, which includes copies of the diagnostic tests done to confirm the index VTE. The dossier will be reviewed by the CEC. Instructions for completing the dossier package will be provided in the outcome reporting manual. Due to logistical constraints, adjudication of index events will be performed after randomization; hence, the adjudicated result will not be used to qualify the subject for the study, but rather to subsequently define the outcome analyses sets.

The index event package must also contain copies of test reports confirming the subject's cancer diagnosis. The investigational site should ensure that any personal subject identification other than subject number and initials are removed from the index event dossier.

Based on the inclusion criterion that long term treatment with LMWH is intended to be given, it is expected that a large proportion of subjects will meet the criteria for active cancer. Nevertheless, the percent of subjects with active cancer will be monitored during the study by a medical monitor who will report to the SMCC chair. If necessary, the SMCC will take appropriate actions to ensure that the proportion of subjects with active cancer is sufficient (ie, > 75%) to draw valid conclusions in the active-cancer population

6.2. Day 1/Randomization

Before randomization, the Investigator will ensure that all protocol-specified pre-randomization requirements and procedures are met and/or completed. For subjects who meet all the inclusion criteria and none of the exclusion criteria, the following will be performed on the day of randomization, prior to actual randomization.

- Complete the IXRS Randomization Visit worksheet including review of subject's age, bleeding risk profile, body weight, calculated CrCL, and concomitant medications;
- Record vital signs (sitting BP and heart rate) and weight;
- Assess and record ECOG Performance Status (see Appendix 17.6 for the ECOG performance scale);
- Collect serum sample for archiving by QLabs for later testing if necessary. Use the QLabs pre-dose Day 1 kit and ship the sample to QLabs;
- Record the following local laboratory results in the eCRF:
  - Serum chemistry
    - Total bilirubin (direct and indirect)
    - Alanine transaminase (ALT)
    - Aspartate transaminase (AST)
    - Alkaline phosphatase (ALP)
    - Serum creatinine
    - CrCL

- Hematology and platelet count

- Hematocrit
- Hemoglobin
- White blood cell (WBC) count with differential
- Platelet count

If all procedures and tests done before randomization confirm the subject's eligibility for the study, access the IXRS, register the subject for study qualification, and obtain the subject identification number.

The following activities and/or assessments will be performed at/during randomization:

- Record AEs and treatments (drug and non-drug) given for AEs;
- Record prior medications taken within 30 days before randomization;
- Record date and time for Day 1 dose of study drug;
- Dispense study drug (dalteparin or edoxaban) and record amount (number of tablets and syringes) dispensed;
- Explain the study medications and the proper daily dosing to the subject using the study medication dosing calendar, and confirm that the subject understands the proper daily dosing of study medication, including when to stop LMWH and begin edoxaban dosing;
- Instruct subject to bring all medications including study drugs to each study visit;
- Provide subjects with a patient information booklet, which will contain the following information:
  - The study outline in layman’s terms;
  - The local medical contact person and emergency telephone number;
  - The visit schedule provided by the IXRS (fax or email with dates of telephone and/or hospital visits);
  - How to recognize and report signs and symptoms of possible recurrent symptomatic PE/DVT or bleeding;
  - Instructions to keep empty medication packages;
  - How to use the study medication.
- Provide subjects with a subject identification safety card and a prohibited medication card.

Investigators will maintain a confidential subject identification code list of names of all the subjects randomized to study to allow the Investigator to reveal the identity of any subject when necessary.

6.3. Treatment Period

The treatment period begins with the first dose of LMWH (dalteparin or other LMWH depending on randomized treatment assignment) after randomization and ends with the last dose of study drug at the time of permanent discontinuation of study drug. During the treatment period, the subject will be instructed to bring all study drug supplies to each scheduled (every 3 months) study assessment. Outcome and other event reporting (eg, VTE, bleeding, AEs) will be done throughout the study as soon as site personnel learn of the event. Recording of AEs and treatments (drug and non-drug) given for AEs will be done throughout the study.

Subjects who permanently discontinue study drug will be followed for efficacy and safety outcomes and SAEs by visit or telephone contact at least once every 3 months until Month 12, except as noted in Section 3.1.2.1. If the subject has an on-site visit, obtain vital signs and any laboratory assessments deemed appropriate by the Investigator. Ideally, all subjects should have their final EOT post-randomization visit completed in person either in-clinic or home visit.

6.3.1. Day 31 (± 3) Visit

At Day 31 following randomization, all subjects should be seen by qualified medical personnel for the following procedures:

- Record concomitant medications and any interruptions in chemotherapy treatment due to a VTE or bleed event;
- Assess study drug dosing compliance;
- Record any interruptions of edoxaban or dalteparin with the date of last dose and the date of the first dose of resumption of drug;
- Assess for AEs and outcome events;
- Capture healthcare resource utilization as appropriate;
- Assess ECOG performance status;
- Monitor and record hemoglobin/hematocrit, platelet counts, weight, serum creatinine, creatinine clearance, and P-gp inhibitor use and determine if a study drug dose adjustment is necessary;
- Dispense study medications and down-titrate dalteparin subjects to maintenance dose.

6.3.2. Months 3, 6, and 9 (± 7 days)

All subjects should be seen by qualified medical personnel for the following procedures:

- Record concomitant medications and any interruptions in chemotherapy treatment due to a VTE or bleed event;
- Assess study drug dosing compliance;

- Record any interruptions of edoxaban or dalteparin with the date of last dose and the date of the first dose of resumption of drug;
- Assess for AEs and outcome events;
- Capture healthcare resource utilization as appropriate;
- Assess ECOG performance status;
- Monitor and record hemoglobin/hematocrit, platelet counts, weight, serum creatinine, creatinine clearance, and P-gp inhibitor use and determine if a study drug dose adjustment is necessary;
- Liver function test monitoring:
  - Record (or collect a serum sample for) transaminase (ALT/AST), alkaline phosphatase, and bilirubin levels
- Dispense study medications.

6.4. End of Treatment/Month 12 (± 7 days)

All subjects should be seen by qualified medical personnel for the following procedures at Month 12 or whenever study treatment is permanently discontinued. Subjects permanently discontinuing study treatment before Month 12 will still be followed until Month 12 or the global EOT date whichever occurs first.

- Record concomitant medications and any interruptions in chemotherapy treatment due to a VTE or bleed event;
- Collect all unused study drug and review the dosing calendar, if one was used;
- Assess study drug dosing compliance;
- Record any interruptions of edoxaban or dalteparin with the date of last dose and the date of the first dose of resumption of drug;
- Count unused edoxaban tablets and dalteparin syringes and record in the IXRS drug accountability module;
- Assess for AEs and outcome events;
- Capture healthcare resource utilization as appropriate;
- Assess ECOG Performance Status;
- Update cancer status/stage;
- Liver Function Test monitoring:
  - Record (or collect a serum sample for) transaminase (ALT/AST), alkaline phosphatase and bilirubin.

6.5. Follow-Up

Not applicable.

6.6. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC.

A deviation to any key protocol procedures, or waiver to any stated eligibility criteria will not be allowed except as noted below and where necessary to eliminate immediate hazard(s) to the subject.

Subjects for whom experimental anticancer treatment is instituted after randomization to the cancer VTE trial will remain in the study and followed for 12 months or the global EOT date, whichever occurs first. The decision whether to discontinue the VTE study treatment will be at PI discretion according to local regulations.

Sponsor must be notified of any unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits).

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

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

The Investigator should notify the IECs/IRBs of deviations from the protocol in accordance with local procedures.

7. OUTCOME ASSESSMENTS

Subjects with suspected recurrent PE/DVT will undergo objective testing to assess the recurrent episode. In subjects with bleeding additional examinations will be done if deemed necessary by the investigator (eg, hematology blood sample, diagnostic imaging/scoping). In subjects with other suspected outcomes such as death, cardiovascular events, or other thrombotic events the diagnostic work-up will be conducted according to the hospital routine.

For all suspected events an adjudication dossier must be prepared for shipment to the CEC. This dossier will contain the following documentation:

- copies of all diagnostic imaging;
- the relevant adjudication worksheets;
- other clinically relevant notes/hospital letters/ laboratory reports/medical records.

Details regarding the definitions of the study outcomes and how they will be assessed are provided in the CEC Charter. The requirements for testing and reporting are provided in the Outcome Reporting Manual and will be provided to all sites.

7.1. Primary Outcome Variable(s)

The primary study outcome is the composite of recurrent VTE and major bleeding.

Recurrent VTE is either:

- symptomatic confirmed (new) DVT or (new) PE;
- unsuspected (new) proximal DVT
  - Unsuspected DVT is a DVT coincidentally detected during other investigations (eg, abdominal or pelvic CT for cancer staging). This DVT will only be included as an outcome if it concerns a (new) clot located in the popliteal or more proximal leg veins. A thrombus detected in the IVC or iliac veins on an abdominal or pelvic CT does not require additional confirmation. A thrombus detected in the common femoral vein or more distal veins can only be confirmed if CUS (or venography) diagnostic criteria are also met.
- unsuspected (new) PE;
  - unsuspected PE is an embolism coincidentally detected during other investigations (eg, CT for cancer staging), that involves segmental or more proximal pulmonary arteries.
- fatal PE (including unexplained death for which PE cannot be ruled out).

Major bleeding is defined as overt bleeding and:

- associated with a decrease in hemoglobin of ≥ 2 g/dL, or
- leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood, or
- occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- contributing to death.

7.2. Secondary Outcome Variable(s)

Secondary outcome variables include:

- Recurrent VTE;
- Major bleeding;
- CRNM bleeding;
- Major + CRNM bleeding;
- Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE -related death;
- Mortality from all causes;
- Recurrent DVT;
- Recurrent PE;
- Healthcare resource utilization for potential recurrent VTE and bleed events.

7.3. Other Outcome Variable(s)

Other outcome variables include:

- Cardiovascular events (myocardial infarction, stroke, SEE [see Appendix 17.5.1]);
- Thrombotic events at other locations (see Appendix 17.5.2);
- Reason for permanent early discontinuation of study drug.

8. PHARMACOKINETIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Variable(s)

Not applicable.

8.2. Pharmacodynamic (PD) Variable(s)

Not applicable.

8.3. Biomarker and Exploratory Variable(s)

Not applicable.

9. SAFETY ASSESSMENTS

9.1. Adverse Events

This study will follow a targeted approach to AE and SAE reporting. All AEs occurring after the subject signs the ICF and through Month 12 or the global EOT date, whichever occurs first (see Sections 4.2.2.1 and Section 6.4), whether observed by the Investigator or reported by the subject, will be recorded on the Master Event/AE page of the CRF if they fulfill 1 of the following criteria: 1) meet seriousness criteria (see Section 9.4.2); 2) result in interruption or discontinuation of study drug (edoxaban or dalteparin); 3) meet criteria as a study outcome (see Section 3.1.4); or 4) an event of special interest (see Section 9.3).

All laboratory, vital sign, or electrocardiogram (ECG) values should be evaluated by the Investigator regarding clinical significance. Isolated abnormal laboratory results or vital sign findings or ECG findings should be reported as AEs if they are symptomatic, result in study drug discontinuation, require corrective treatment, or are otherwise defined as an AE of special interest (AESI). Clinically significant abnormal laboratory findings associated with the subject's cancer or other pre-existing conditions will not be reported as AEs or SAEs unless judged by the Investigator as more severe than expected for the subject's condition and meet the criteria for targeted AE and SAE reporting. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history. All SAEs are to be reported according to the procedures in Section 9.5 Serious Adverse Event Reporting-Procedure for Investigators.

All SAEs occurring after informed consent for general study participation is obtained are to be reported according to the procedures in Section 9.5. Always report the diagnosis as an AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. A pre-planned (prior to signing the Informed Consent Form) procedure or treatment requiring hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for Definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. When a subject dies from disease progression of pre-existing cancer with no other immediate causes, "disease progression" should be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

At each visit, the Investigator or appropriately qualified designee will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each

study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs 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.

9.2. Safety Outcomes

9.2.1. Bleeding Outcomes

All suspected bleeding events, irrespective of the clinical relevance assessed by the Investigator, must be reported and will be reviewed and classified by the CEC as major, clinically relevant non major, nuisance or no bleeding event.

Details regarding the classification of bleeding events and how these events will be assessed are provided in the CEC Charter. The requirements for reporting bleeding events are provided in the Outcome Reporting Manual and will be provided to all study sites.

9.3. Events of Special Interest

9.3.1. Combined Elevations of Aminotransferase 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 without evidence of cholestasis (ALP > 2 x ULN 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 of liver laboratory abnormalities, or evidence of liver dysfunction, it is important to ensure that the nature and the extent of liver injury is identified and study subjects are monitored until the liver laboratory assessments return to normal. (Please refer to Section 4.2.2.1).

9.4. Definitions

9.4.1. Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

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

9.4.2. Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

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

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

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

Note:

The following are not considered AEs or SAEs:

- Hospitalization for a pre-planned procedure or diagnostic tests (including for cancer staging, eg, CT scan, Magnetic Resonance Imaging, gastroscopy, cystoscopy, bronchoscopy, etc) or treatment for pre-existing conditions (eg, chemotherapy, radiation therapy) should NOT be reported as SAEs;

- Hospitalization for diagnostic work-up or treatment of worsening underlying cancer or complications of cancer treatment (eg, work-up for febrile neutropenia, transfusion for anemia, MUGA scan to rule out cardiomyopathy) should NOT be reported as SAEs.

9.4.3. Adverse Event Severity

The following definitions should be used to assess intensity of AEs per the NCI CTCAE criteria:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

9.4.4. Causality Assessment

The Investigator should assess causal relationship between an adverse event and the study product LMWH/edoxaban 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 study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).
  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- 2 = Not Related:
  - The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding the Study Product

- 1 = Dose Not Changed: No change in study drug dosage was made.
- 2 = Drug Withdrawn: The study product was permanently stopped.
- 3 = Dose Reduced: The dosage of study product was reduced.
- 4 = Drug Interrupted: The study product was temporarily stopped.

- 5 = Dose Increased: The dosage of study product was increased.

9.4.6. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The subject fully recovered from the adverse event with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the adverse event are still present and observable.
  - Include sequelae/residual effects.
- 3 = Not Recovered/Not Resolved
  - The adverse event itself is still present and observable.
- 4 = Fatal
- 5 = Unknown

9.4.7. Other Action Taken for Event

- 1 = None.
  - No treatment was required.
- 2 = Medication required.
  - Prescription and/or over-the-counter medication was required to treat the adverse event.
- 3 = Other.

9.5. Serious Adverse Event Reporting–Procedure For Investigators

All AEs, SAEs, AESIs, and study outcomes will be captured in the eCRF.

Study outcomes are clinically anticipated events and will be periodically reviewed by the DMC to ensure prompt identification of any clinically concerning safety issues. Study outcomes (suspected recurrent DVT or PE, bleeding, MI, stroke, SEE [see Appendix 17.5.1], and thrombotic events at other locations [see Appendix 17.5.2]) will be exempted from expedited safety reports of suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities, Investigators, IECs, and IRBs. All SAEs resulting in death, regardless of whether they are waived endpoint events, will be captured in the Sponsor's global safety database.

The following types of events should be reported by the Investigator in eCRF within 24 hours of awareness to support expedited safety reporting:

- SAEs (see Section 9.4.2 for definition)
- Liver enzyme abnormalities/liver dysfunction events [ALT or AST > 3x ULN with simultaneous TBL > 2 x ULN] without evidence of cholestasis (ALP > 2

x ULN) and without alternative etiology for hepatocellular damage (both serious and non-serious).

Call Quintiles (telephone number will be provided per country, per region; please refer to Study Manual for an appropriate phone number) for any questions on SAE reporting. Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

In the event that eCRF is unavailable, report SAEs by faxing the paper Daiichi Sankyo Serious Adverse Event Report (SAVER) Form to Quintiles using the provided fax cover sheet and the appropriate fax number provided for your country (please refer to Study Manual for an appropriate fax number). Once eCRF becomes available, please enter SAEs reported on the SAVER Form into eCRF as soon as possible.

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

Daiichi Sankyo and/or Quintiles will inform Investigators, IRBs (Institutional Review Board)/ECs, and regulatory authorities of any Suspected Unexpected Serious Adverse Event Reactions (SUSARs) occurring in other study centers or other Daiichi Sankyo studies of the investigational product (excluding waived study outcomes per Section 9.5), as appropriate per local reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the investigational product, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

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

9.6. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving investigational product and through Month 12 or the global EOT date, whichever occurs first, or, within 30 days of last dose if it occurred less than 30 days of the global EOT date.

Although pregnancy is not technically an adverse event, 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 female subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, 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 SAEs outlined in Section 9.5.

9.7. Clinical Laboratory Evaluations

Local laboratory results and reference ranges for the analytes outlined in Sections 6.2, 6.3.1, 6.3.2, and 6.4 will be recorded in the eCRF.

9.8. Vital Signs

Vital sign data will consist of heart rate, BP, and height. Weight will also be recorded in order to make determinations regarding study drug dose adjustments.

9.9. Electrocardiograms

Routine ECGs are not required but will be recorded in the eCRF when appropriate.

9.10. Physical Findings

A physical examination, conducted prior to or at the time of randomization by the Investigator or other qualified health care provider designated by the Investigator, will consist of assessment of each of the relevant major body systems.

9.11. Other Safety Assessments

Other safety assessments will be conducted as necessary.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. Analysis Sets

11.1.1. Randomized Analysis Set

The randomized analysis set includes all subjects randomized to treatment.

11.1.2. Modified Intention-to-Treat Analysis Set

The mITT Analysis Set includes all randomized subjects who receive at least 1 dose of study drug[1].

11.1.3. Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set includes all randomized subjects who receive at least 1 dose of study drug, who have not experienced treatment misallocation, and for whom the index DVT or PE event at baseline was confirmed by the CEC. Treatment misallocation is defined as a subject taking incorrect treatment during the entire study period.

11.1.4. Safety Analysis Set

The Safety Analysis Set includes all randomized subjects who receive at least 1 dose of randomized study drug. Analyses will be based on the randomized treatment, unless a subject inadvertently receives the incorrect drug during the entire study, in which case, the subject will be grouped according to the treatment actually received.

11.2. General Statistical Considerations

The efficacy analyses will be based on the mITT and PP Analysis sets.

The safety analyses will be based on the Safety Analysis Set.

The data analysis will be performed by a CRO under the guidance of the study biostatistician. Data analyses will be performed using software SAS Version 8.0 or higher.

11.3. Study Population Data

The number of subjects in each analysis set will be presented by treatment group. Subjects excluded from the analysis sets will be listed and summarized by treatment group and reason for exclusion. The number and percentage of randomized subjects who discontinued treatment prematurely will be tabulated by main reason for discontinuation and treatment group. Demographic and baseline characteristics (including risk factors) will be summarized by treatment group using descriptive statistics. No statistical tests will be performed.

[1] Study drugs include the LMWH prescribed by the PI as the edoxaban lead-in, edoxaban, and dalteparin.

11.4. Outcome Analyses

11.4.1. Primary Outcome Analyses

The primary outcome analysis will be based on the mITT Analysis Set. In this analysis, the time to the first event of the composite primary outcome (recurrent VTE [symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, unsuspected PE, fatal-PE] or major bleed) will be analyzed using a Cox's proportional hazard model including treatment group, and the stratification factors as covariates. The time to first event is defined as the time (days) from the day of randomization to the first event experienced by a subject during the 12-month study period. Subjects who do not have a primary outcome during the 12-month study period will be censored at Day 365, or the last day the subject had a complete assessment for study outcomes, or the global EOT date, whichever comes first. Subjects lost to follow-up, subjects who died because of reasons other than DVT/PE, or subjects who withdrew informed consent before the end of the 12-month treatment period and who did not have a primary outcome, will be censored at the last day the subject had a complete assessment for study outcomes. The LMWH/edoxaban-to-comparator Hazard Ratio will be computed with 95% CI (two-sided testing), based on this model. LMWH/edoxaban will be considered non-inferior to comparator if the upper limit of the CI is < 1.5.

The assumption of proportional hazards will be checked using graphical methods as log (log)-plots and plots of scaled Schoenfeld residuals for the primary analysis. If the assumption is seriously violated, then a logistic model including treatment group and the stratification factors as covariates will be used. The impact of selected baseline covariates on the primary outcome will be described by calculating adjusted Hazard Ratios and corresponding 95% CI of the treatment effect.

The frequencies of the each components contributing to the primary outcome will be described.

The following sensitivity analyses will be performed for the Primary Outcome:

- On-Treatment events based on the PP Analysis Set will be analyzed using the counting process approach of the Cox proportional hazards regression model including treatment group, and the stratification factors as covariates. An On-Treatment event is defined as the event occurring during the time period the subject is taking study drug up to 3 days after their last dose for that time period. Only events occurring prior to or on Day 365 will be included into this analysis. Subjects who do not experience an On-Treatment event will be censored at Day 365, or the time study drug is permanently discontinued plus 3 days or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global end of treatment, whichever comes first.
- Events occurring during the first 6 months (180 days) based on the mITT Analysis Set will be analyzed using the same statistical model as the primary analysis of the primary outcome. The time to event is defined as the time (days) from the randomization to the first event during the first 6 months after

randomization. Subjects who do not experience an event until Day 180 will be censored at Day 180, or the time study drug is permanently discontinued or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, whichever comes first.

11.4.2. Superiority Analysis of the Primary Outcome

If non-inferiority in the primary outcome is established, LMWH/edoxaban will be compared to dalteparin for superiority (α=0.05, two-sided) with regard to the time to an event in the composite clinical outcome of recurrent VTE (symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, unsuspected PE, and fatal-PE) or major bleed during the 12-month study period. This analysis will be based on the mITT Analysis Set using the same proportional hazard model as for the primary outcome.

11.4.3. Secondary Efficacy Outcome Analyses

Summary statistics will be provided for following efficacy outcomes:

- recurrent VTE;
- event-free survival, the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE -related death;
- recurrent DVT;
- recurrent PE.

The impact of cancer status on the primary outcome will also be assessed.

A description of all planned analyses will be incorporated into the SAP.

11.5. Pharmacokinetic Analyses

Not applicable.

11.6. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

11.6.1. Analysis of the Primary Safety Outcome

The primary analysis of the primary safety outcome is based on an "On-Treatment" approach. The "on-treatment" major bleeding events will be compared between treatment groups for superiority (α=0.05, two-sided) for subjects in the Safety Population, using the counting process approach of the Cox proportional hazards regression model including treatment group, and the stratification factors as covariates. However, subjects will be censored 3 days after the day of permanent study medication discontinuation.

11.6.2. Analysis of Secondary Safety Outcomes

Incidence and Hazard Ratio (with 95% CI) for the following outcomes will be calculated based on the Safety Analysis Set and On-Treatment-approach using the same counting

process approach of the Cox proportional hazards regression model as for the primary safety outcome analysis:

- Major bleeding;
- Clinically relevant non-major bleeding;
- Major + clinically relevant non-major bleeding;
- Mortality from all causes.

Healthcare resource utilization for potential recurrent VTE and bleeding events will be analyzed separately.

11.6.3. Exploratory Analyses for Safety Outcomes

The incidence of cardiovascular events (myocardial infarction, stroke, SEE) and thrombotic events at other locations will be summarized by treatment.

The reason for permanent early discontinuation of study drug will be summarized by treatment group.

Details are specified in the SAP.

11.6.4. Adverse Event Analyses

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Any AE that occurs during the study is a study AE. Treatment-emergent adverse events (TEAEs) are defined as an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state. The incidence of TEAEs will be presented for the Safety Analysis Set by treatment group, by relationship to the study drug, and by severity. Frequent TEAEs (reported by at least 5% of subjects in any treatment group) will be summarized by treatment group. Adverse events that start or worsen after the third day following the calendar date of any "last dose" and before the date of the next "first dose" are defined as post-treatment AEs. Because a subject can have study drug interruptions, it will be possible to have a post-treatment AE that occurs at an earlier calendar date than a TEAE.

The incidence of death, SAEs, drug-related SAEs, and AEs leading to discontinuation of study drug will be summarized by treatment group. All AEs will be included in a data listing and a listing to display the coding of AEs will be prepared as well.

11.6.5. Clinical Laboratory Evaluation Analyses

The clinical laboratory evaluations at each scheduled visit and the change from baseline will be summarized for the Safety Analysis Set by treatment group. Shift tables (low, normal, and high) will be provided for each treatment group for selected clinical laboratory parameters. The number and percentage of subjects with clinically relevant abnormal clinical laboratory values while on study drug will be calculated for each treatment group for selected clinical laboratory parameters. All abnormal clinical laboratory values will be presented in a listing.

11.6.6. Vital Sign Analyses

Vital signs at each evaluation point and the change from baseline will be summarized for the Safety Analysis Set by treatment group. The number and percentages of subjects with abnormal vital signs while on study drug will be summarized by treatment group.

11.6.7. Physical Finding Analyses

Abnormalities in physical examinations by body system will be listed.

11.7. Other Analyses

11.8. Interim Analyses

No formal interim analysis is planned. Risk-benefit will be evaluated by the DMC, which will give recommendations on a regular basis to the Executive Committee. Access to interim tabular risk-benefit data will be restricted. The procedures of the DMC will be described in its charter.

11.9. Data and Safety Monitoring Board

An independent DMC will be created to further protect the rights, safety, and well-being of subjects who will be participating in this study. The DMC will be composed of qualified scientists, who are not Investigators in the study and not otherwise directly associated with the Sponsor. The DMC will be described in detail in the DMC Charter.

Activities of the DMC will be documented. This documentation will include data summaries and analyses provided to the committee as well as minutes of the meeting.

The DMC can recommend study or treatment regimen/group termination to the Executive Committee based on pre-specified concerns described in the DMC Charter.

11.10. Subgroup Analyses for Efficacy and Safety

Exploratory subgroup analyses, relative to primary study outcomes and key safety outcomes may include, but are not limited to, treatment group comparisons within subject characteristics (age, gender, geographic region, dose adjustment) as described in the SAP.

11.11. Sample Size Determination

Assuming a hazard ratio of 1, a total of 191 overall primary events are projected to accrue in the mITT analysis set which will ensure at least 80% power for the primary analysis at a non- inferiority margin for the hazard ratio of 1.5 and a Type I error of 0.05 (two-sided).

Assuming a primary combined outcome rate (recurrent VTE or major bleed) of 20.0%, a total of 1000 subjects are expected to be randomized to study treatment in order to accrue 191 overall primary events in the mITT analysis set.

12. DATA INTEGRITY AND QUALITY ASSURANCE

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

This study will utilize Quintiles Data-driven Trial Execution (DTE), which is Quintiles model for risk-based monitoring.

Quintiles' DTE and Daiichi Sankyo will begin with a risk assessment to evaluate the scientific and operational risks of the study. During this risk assessment key data points for the study will be identified and the optimum method for monitoring (eg, remote, on-site, and/or centralized monitoring processes) each key data point will be determined. Key data points are data items that are critical to study analysis, indicate if the objectives of the study have been met, support patient safety, and/or are deemed as a priority for monitoring.

12.1. Monitoring and Inspections

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

The monitor is responsible for conducting both onsite and remote monitoring visits 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 frequency of monitoring visits will be dependent on the activities at the site. At a minimum the monitor will visit active sites on an annual basis. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

Transcription-Based source data verification (SDV) is a strategic monitoring task that will be used to detect transcription errors between the source documents and the eCRF. SDV will be performed on 100% of data for a sample of enrolled subjects at each site. The sample size may be increased where issues are identified.

Source data review (SDR) is an on-site monitoring process in which source documentation is reviewed to ensure that the site's process for documenting source notes is appropriate and that the site is adhering to the requirements of the protocol. The SDR will be performed on the same subjects as SDV. The SDR may be performed on additional subjects where issues are identified.

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

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

Monitoring triggers consisting of essential operational data elements will be used to assess site performance, data quality, and patient safety. Monitoring triggers may independently trigger a site contact or monitoring visit.

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 (eg, pharmacy, drug storage areas, laboratories, etc) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.2. Data Collection

The eCRF completion and query resolution should be kept current to enable the monitor to review the subject's status throughout the course of the study and to enable review of the data by Clinical Data Management.

12.3. Data Management

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

To ensure the quality of clinical data across all subjects and sites, two levels of review will be performed:

The first level review will comprise of traditional data management review. The second level review is a manual check for clinical congruency of the data.

Both the first and second levels of the Clinical Data Management review will be performed on subject data according to specifications agreed by Sponsor and CRO. Data will be vetted both electronically and manually; eCRFs data will be electronically vetted by programmed data rules within the Electronic Data Capture (EDC). Queries generated by rules and raised by reviewers will be generated and resolved within the EDC application. During these reviews, subject data will be checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the Clinical/Data Management review process, eCRFs queries will be raised and resolved within the EDC application.

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

Serious AEs in the clinical database will be reconciled with the safety database.

All Adverse Events and medical history entries will be coded using MedDRA. Concomitant medications, when necessary, will be coded using the World Health Organization Drug Reference (WHODRUG) List.

12.4. Study Documentation and Storage

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

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

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

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

12.5. Record Keeping

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

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with Quintiles. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

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

14. PUBLICATION POLICY

A site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until 1 year after the study has ended, whichever occurs first. Therefore, the site will have the opportunity to publish the results of the study, provided that Daiichi Sankyo has had the opportunity to review and comment on the site's proposed publication prior to its being submitted for publication with the prior advice of Daiichi Sankyo Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

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 protocol. A protocol amendment may be implemented after it has been approved by the IRB/EC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/EC within 5 working days. The Sponsor will enssure the timely submission of amendments to regulatory authorities.

15.2. Address List

15.2.1. Sponsor

Daiichi Sankyo Pharma Development
399 Thornall Street
Edison, NJ 08837
Phone: 732-590-5000

15.2.2. CRO

Quintiles, Inc.
4820 Emperor Blvd
Durham, NC 27703
Phone: 919-998-2000

15.2.3. Academic Research Organization (ARO)

ITREAS
Wg-Plein 188
Amsterdam 1054 SC
The Netherlands
Phone: +31 20 233 0563

16. REFERENCES

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17. APPENDICES

17.1. Additional Information on Investigational Products

17.1.1. Fragmin Package Insert

The Fragmin (dalteparin) package insert can be accessed at the following link: http://www.medicines.org.uk/emc, then typing Fragmin in the search field.

17.2. Transition from Edoxaban to Other anticoagulants

17.2.1. Edoxaban to VKA

Discontinue edoxaban and administer a parenteral anticoagulant and VKA at the time of the next scheduled edoxaban dose. Once a stable INR $\geq$ 2.0 is achieved, the parenteral anticoagulant must be discontinued and the VKA continued.

17.2.2. Edoxaban to non-VKA Oral Anticoagulants

Discontinue edoxaban and start the non-VKA anticoagulant at the time of the next scheduled dose of edoxaban.

17.2.3. Edoxaban to Parenteral Anticoagulants

Discontinue edoxaban and start the parenteral anticoagulant at the time of the next scheduled dose of edoxaban.

17.3. Prohibited Concomitant Medications

Specifically excluded concomitant medications and cautions regarding other concomitant medications are provided below. The list in this appendix reflects exclusionary concomitant medications at the beginning of the study. If there are changes to this list during the study, the changes will be provided as an update to this appendix, but will not be considered a protocol amendment.

17.3.1. Antiplatelet Drugs

Dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or IV antiplatelet drug) is prohibited while on study drug. If a clinical indication for dual antiplatelet therapy arises after randomization (eg, placement of an intracoronary stent), study drug should be interrupted and use of open-label LMWH/VKA is permitted at the physician's discretion.

Use of any antiplatelet medication, including aspirin, as single agent antiplatelet therapy is allowed while on study drug.

It is strongly encouraged to restrict the dose of aspirin (if indicated) to ≤ 100 mg daily, although higher doses are permitted for a strong clinical indication (eg, development of an acute MI).

Examples of non-aspirin oral antiplatelet agents include the following:

- Thienopyridines: clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel (Effient™)
- Dipyridamole: Persantine®, Aggrenox®
- Pentoxifylline (Trental®)
- Sulfinpyrazone (Anturane®)
- Ticagrelor (Brilinta®)
- Cilostazol (Pletal®)

IV antiplatelet agents include the following:

- Glycoprotein IIb/IIIa inhibitors: Abciximab (ReoPro™), Eptifibatide (Integrilin®), Tirofiban (Aggrastat®)
- PGY12 Inhibitor: Cangrelor
- Dextran

17.3.2. Oral Anticoagulants Other Than Study Drug

Oral anticoagulants including vitamin K antagonists (eg, warfarin), Factor IIa inhibitors (eg, dabigatran), and FXa inhibitors (eg, rivaroxaban, apixaban) after randomization are

prohibited (unless used to bridge a temporary study drug interruption). The only allowed oral antithrombotics are the study drugs.

17.3.3. Parenteral Anticoagulants

Parenteral anticoagulants such as heparin, LMWHs, direct thrombin inhibitors, and FXa inhibitors are prohibited except as specifically outlined in the protocol. For instance, LMWHs are allowed as lead-in therapy prior to edoxaban administration. Examples of prohibited parenteral anticoagulant medications, when used contrary to protocol specifications, include the following:

- Low molecular weight heparins: dalteparin (Fragmin®), tinzaparin (Innohep®, Logiparin®), reviparin (Clivarin®), nadroparin (Fraxiparine®), ardeparin (Normiflo®), certoparin (Sandoparin®), parnaparin (Fluxum®)
- Direct thrombin inhibitors: bivalirudin (Angiomax®), argatroban (Acova®), desirudin (Ipravask®), lepirudin (Refludan®)
- FXa inhibitors: fondaparinux (Arixtra®)

17.3.4. Intravenous Fibrinolytics

Examples of fibrinolytics include the following:

- Tissue plasminogen activator (alteplase, Activase®)
- TNK (tenecteplase, TNKase®)
- rPA (reteplase, Retavase®)
- Streptokinase (Streptase®)
- Anistreplase (Eminase®)

If a subject requires treatment with a fibrinolytic agent, then study drug must be interrupted while the subject is taking the fibrinolytic drug and at least 24 hours after administration of a fibrinolytic agent.

17.3.5. NSAIDs (Excluding Aspirin)

While on study drug, NSAIDs cannot be taken for ≥ 4 days per week. Less frequent use of NSAIDs is permitted while on study drug. However, the Investigator should weigh the benefit/risk of NSAID use in combination with an oral anticoagulant for the individual subject. Examples of NSAIDs include the following:

Aceclofenac	Acemetacin	Alclofinac
Amtolmetin	Axapropazone	Benoxaprofen
Bromfenac	Bufexamac	Carprofen
Clonixin	Dexibuprofen	Dexketoprofen
Diclofenac	Diclofenac/Hyaluronic Acid	Diflunisal
Dipyrone	Droxicam	Etodolac
Etofenamate	Felbinac	Felbufen
Fenoprofen	Fentiazac	Floctafenine
Flufenamic Acid	Flurbiprofen or fluribuprofen	Hydrocodone/Ibuprofen
Ibuprofen	Indomethacin	Indoprofen
Isoxicam	Ketoprofen	Ketorolac
Lansoprazole/Naproxen	Lornoxicam	Loxoprofen
Meclofenamate	Mefanamic Acid	Meloxicam
Morniflumate	Nabumetone	Naproxen
Niflumic Acid	Nimesulide	Oxaprozin
Oxycodone/Ibuprofen	Phenylbutazone	Piketoprofen
Pirazolac	Piroxicam	Piroprofen
Prophenazone	Proquazone	Sulindac
Suprofen	Tenidap	Tenoxicam
Tiaprofenac Acid	Tolmetin	Zomepirac

17.3.6. COX-2 Inhibitors

While on study drug, COX-2 inhibitors cannot be taken for ≥ 4 days per week. Less frequent use of COX-2 inhibitors is permitted while on study drug. However, the Investigator should weigh the benefit/risk of COX-2 inhibitor use in combination with an oral anticoagulant for the individual subject. Examples of COX-2 inhibitors include the following:

Celecoxib	Parecoxib
Artilog	Dynastat
Celecox	Rofecoxib
Celebra	Arofex
Celebrex	Ceoxx
Solexa	Coxxil
Etoricoxib	Dolcoxx
Arcoxia	Miraxx
Lumiracoxib	Vioxx
Lumirelax	Vioxxalt
Lumrelax (FM)	Valdecoxib
Lumirem	Bextra

17.3.7. P-gp Inhibitors

Concomitant use of protease inhibitors (such as ritonavir, nelfinavir, indinavir, and saquinavir) anticipated to continue during the course of the study is prohibited. Concomitant use of certain macrolide antibiotics (erythromycin, azithromycin, and clarithromycin) and azole antifungals (ketoconazole and itraconazole) are also prohibited at the time of randomization, but subsequent use of these agents is permitted after randomization with appropriate dose reduction of edoxaban to 30 mg QD. Once treatment with these P-gp inhibitors is complete, the full 60 mg edoxaban dose should be resumed.

The following common P-gp inhibitors that might be administered to study subjects require a reduction in the edoxaban dose to 30 mg QD:

- Tyrosine kinase inhibitors: imatinib, nilotinib, lapatinib, sunitinib, criozitinib, vandetanib
- Hormonal agents: tamoxifen, enzalutamide, abiraterone,
- Immuno-modulating agents: cyclosporine, tracolimus, dexamethasone

Once treatment with these P-gp inhibitors is complete, the full 60 mg edoxaban dose should be resumed.

Note: Other agents in these classes may be administered concurrently without reducing the edoxaban dose.

17.4. Precautions and Dose Modifications for Dalteparin

Month 1 – Dalteparin Doses by Weight

Body Weight (kg)	Scheduled Dalteparin Dose (IU)
≤ 46	7500
47 to 56	10000
57 to 68	12500
69 to 82	15000
≥ 83	18000

Months 2-12 – Dalteparin Doses by Weight

Body Weight (kg)	Scheduled Dalteparin Dose (IU)
≤ 56	7500
57 to 68	10000
69 to 82	12500
83 to 98	15000
≥ 99	18000

Precautions and Dose Modifications

Month 1:

In the case of chemotherapy-induced thrombocytopenia, the dalteparin dose should be adopted as follows:

- In subjects receiving dalteparin who experience platelet counts between 50,000 and 100,000/mm^3, the daily dose of dalteparin should be reduced by 2,500 IU until the platelet count recovers to ≥100,000/mm^3.
- In subjects receiving dalteparin who experience platelet counts < 50,000/mm^3, dalteparin should be discontinued until the platelet count recovers above 50,000/mm^3.

Months 2-6:

In the case of chemotherapy-induced thrombocytopenia, frequent monitoring of peak anti–FXa levels should be undertaken and the dalteparin dose should be adopted as follows:

- With platelet counts < 50,000/mm^3, dalteparin dosing should be interrupted until the platelet count recovers above 50,000/mm^3.
- For platelet counts between 50,000 and 100,000/mm^3, dalteparin should be reduced as illustrated in the table below in accordance with the subject's weight. Once the platelet count has recovered to > 100,000/mm^3, dalteparin should be re-instituted at full dose.

Table 17.1: Dalteparin Dose Reduction for Platelet Counts Between 50,000 and 100,000/mm^3

Body Weight (kg)	Scheduled Dalteparin Dose (IU)	Reduced Dalteparin Dose (IU)
≤56	7500	5000
57 to 68	10000	7500
69 to 82	12500	10000
83 to 98	15000	12500
≥99	18000	15000

17.5. Definitions of Cardiovascular and Thrombotic Events

17.5.1. Systemic Embolic Event (SEE)

A systemic embolic event is defined as an abrupt episode of arterial insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (eg, atherosclerosis, instrumentation). Arterial embolic events involving the CNS (including the eye), coronary, and pulmonary arterial circulation are not considered SEEs, but will be classified respectively as stroke/TIA, myocardial infarction, and pulmonary embolism. In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusions.

17.5.2. Thrombotic Events at Other Locations

These include:

- Catheter-associated thrombosis
- Cerebral venous and sinus thrombosis
- Retinal vein occlusion
- Upper extremity venous thrombosis
  - axillary, subclavain and brachial vein thrombosis
  - Jugular vein thrombosis
  - Superior caval vein thrombosis
- Abdominal vein thrombosis
  - Splanchnic vein thrombosis
    - Portal vein thrombosis
    - Mesenteric vein thrombosis
    - Splenic vein thrombosis
  - Hepatic vein thrombosis
- Genito-urinary venous thrombosis
  - Renal vein thrombosis
  - Ovarian vein thrombosis
  - Penile vein thrombosis
- Distal deep vein thrombosis
  - distal DVT: tibial veins, peroneal veins
  - muscular vein thrombosis
- Superficial vein thrombosis of the lower or upper limb

17.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead
* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

17.7. Schedule of Events

Table 17.2: Schedule of Events

	Treatment Period							
	Pre-randomization	**Day 1 Randomization**	**Day 31 ± 3 days**	**Month 3 ± 7 days**	**Month 6 ± 7 days**	**Month 9 ± 7 days**	**Month 12 ± 7 days**	**EOT[g] ± 7 days**
Informed Consent	X							
Diagnosis of VTE	X							
Inclusion/Exclusion Criteria	X[a]							
Demographic Information	X							
Medical/Surgical History	X							
Physical Examination[b]	X							
Vital Signs/Weight	X	X						
Cancer Status/Stage	X						X	X
Clinical Assessments and ECOG Performance Status		X	X	X	X	X	X	X
IXRS Randomization		X						
LFT Monitoring[c]		X		X	X	X	X	
Serum Creatinine/CrCL		X	X	X	X	X		
Hematology and Platelet Count		X	X	X	X	X		
Archive Serum Sample[d]		X[c]						
Prior and Concomitant Medication	X	X	X	X	X	X	X	X
AE Reporting[e]		X	X	X	X	X	X	X
Outcome Events Reporting[e]		X	X	X	X	X	X	X
Healthcare Resource Utilization			X	X	X	X	X	X
Study Drug Dispensing[f]		X	X	X	X	X		
Study Drug Compliance			X	X	X	X	X	X
Contact IXRS for study drug assignment or to enter subject status changes[g]		X	X	X	X	X		

	Treatment Period							
	Pre-randomization	**Day 1 Randomization**	**Day 31 ± 3 days**	**Month 3 ± 7 days**	**Month 6 ± 7 days**	**Month 9 ± 7 days**	**Month 12 ± 7 days**	**EOT[g] ± 7 days**

LFT-liver function test; VTE-venous thromboembolism; AE-adverse event(s); IXRS-Interactive web/voice response system; CrCL-creatinine clearance; ALT-alanine transferase; AST-aspartate transferase; EOT-end-of-treatment; ECOG-Eastern Cooperative Oncology Group.

[a] Review inclusion/exclusion criteria and ensure that the subject qualifies with regard to the laboratory tests for exclusion criteria (CrCl , 30 mL/min; Platelet count < 50,000/mm^3.

[b] Physical examination at pre-randomization may be performed by an Investigator or other healthcare provider designated by the Investigator. The physical examination includes vital signs (sitting blood pressure and heart rate), record height, and record body weight.

[c] ALT/AST, total bilirubin, and alkaline phosphatase at randomization and subsequent assessments.

[d] One serum sample will be collected at randomization for archiving.

[e] AE reporting and Outcome Events Reporting should occur throughout the study and not be restricted to specific visits; capture healthcare resource utilization data for potential recurrent VTE and bleed events.

[f] Study drug assigned by the IXRS will be dispensed as a 3-month supply.

[g] All subjects should be seen by qualified medical personnel for the following procedures at Month 12 or whenever study treatment is permanently discontinued. Subjects who discontinue study treatment before Month 12 will still be followed until Month 12, or until the global EOT date, whichever comes first.

CLINICAL STUDY PROTOCOL

A PHASE 3B, PROSPECTIVE, RANDOMIZED, OPEN-LABEL, BLIND EVALUATOR (PROBE) STUDY EVALUATING THE EFFICACY AND SAFETY OF (LMW) HEPARIN/EDOXABAN VERSUS DALTEPARIN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

DU176b-D-U311

IND/EUDRACT NUMBER 63,266/2014-004708-30

VERSION 3.0, 20 JAN 2016

VERSION 2.0, 17 DEC 2015

VERSION 1.0, 15 DEC 2014

DAIICHI SANKYO PHARMA DEVELOPMENT

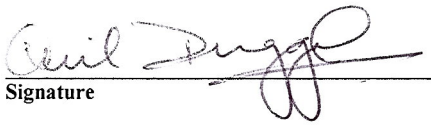
399 THORNALL STREET
EDISON, NJ 08837

INVESTIGATOR AGREEMENT

EDOXABAN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

Sponsor Approval:

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

Anil Duggal, MD	
Print Name	**Signature**
Senior Director, Clinical Development (Cardiovascular)	21 Jan 2016
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

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

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

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

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

PROTOCOL SYNOPSIS

EudraCT/IND Number:	2014-004708-30/63,266
Protocol Number:	DU176b-D-U311
Investigational Product:	Edoxaban (DU-176b)
Active Ingredient(s)/INN:	*N*-(5-Chloropyridin-2-yl)-*N*□-[(1*S*,2*R*,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
Study Title:	A Phase 3b, prospective, randomized, open-label, blind evaluator (PROBE) study evaluating the efficacy and safety of (LMW) heparin/edoxaban versus dalteparin in venous thromboembolism associated with cancer
Short Title:	Edoxaban in Venous Thromboembolism Associated with Cancer (Hokusai VTE Cancer)
Study Phase:	Phase 3b trial
Indication Under Investigation:	Venous thromboembolism associated with cancer
Study Objectives:	Primary Objectives: The primary objective is to demonstrate the non-inferiority of edoxaban (preceded by a short course of LMWH) compared with dalteparin for the prevention of the combined outcome of recurrent venous thromboembolism (VTE) or major bleeding in subjects with VTE associated with cancer during a 12-month study period. If non-inferiority is established, LMWH/edoxaban will be compared with dalteparin for superiority. Secondary Objectives: To compare LMWH/edoxaban with dalteparin with regards to rates of: 1. Recurrent VTE; 2. Major bleeding; 3. Clinically relevant non-major (CRNM) bleeding; 4. Major + CRNM bleeding; 5. All bleeding;

	6. Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death; 7. VTE-related death; 8. Mortality from all causes; 9. Recurrent deep vein thrombosis (DVT); 10. Recurrent pulmonary embolism (PE); 11. Healthcare resource utilization for potential recurrent VTE and bleed events. Exploratory Objectives: To compare LMWH/edoxaban with dalteparin with regards to: 1. Cardiovascular events (myocardial infarction [MI], stroke, systemic embolic events [SEE; see Appendix 17.5.1]); 2. Thrombotic events at other locations (see Appendix 17.5.2) 3. Reason for permanent early discontinuation of study drug.
Study Design:	This is a multinational, prospective, randomized, open-label, blind-evaluator (PROBE), non-inferiority study comparing edoxaban with dalteparin for prevention of the combined outcome of recurrent VTE or major bleeding in patients with VTE associated with cancer. One thousand subjects (1000) will be equally randomized to 1 of the 2 treatment groups. After a subject's eligibility is confirmed, the subject will be stratified by 1) bleeding risk, and 2) the need for dose adjustment, and then randomly assigned via interactive voice/web response system (IXRS) in a 1:1 ratio to treatment with either LMWH/edoxaban or dalteparin (see details in Section 3.1.2. **LMWH/Edoxaban group**: Therapeutic doses of LMWH (subcutaneous [SC]) will be administered for at least 5 days; this 5 day period may include the pre-randomization LMWH (if applicable). The choice of this parenteral LMWH is up to the treating physician. Thereafter, edoxaban will be started orally at 60 mg once daily [QD] (2 × 30 mg tablets) (30 mg QD for subjects requiring dose adjustment) for the remainder of the treatment period.

	Dalteparin group: After randomization, dalteparin will be administered at a dose of 200 IU/kg SC (maximum daily dose 18,000 IU) for 30 days. The 30 day period may include the pre-randomization anticoagulant treatment if dalteparin was used in therapeutic doses. Thereafter (approximately Day 31 forward), dalteparin will be administered at a dose of 150 IU/kg SC (~ 75% - 83% of the initial dose) for the remainder of the treatment period. The intended treatment duration and follow-up for all subjects is 12 months, except for the final subject(s) randomized to the study. Once 1000 subjects are randomized, a global End-of-Treatment (EOT) date will be established that ensures a minimum of 6 months of study treatment and follow-up for the final subject(s) randomized. All subjects will permanently discontinue study treatment on or before the EOT date. After randomization subjects will be assessed at Month 1, Month 3, and quarterly thereafter for up to 12 months until they complete the study. Subjects requiring additional anti-coagulation therapy who complete their treatment and full 12-month post randomization follow-up or whose treatment is truncated due to the global End of Treatment date will be managed according to local practice. Guidance for switching from edoxaban to other anticoagulants is provided in Appendix 17.2. Additional guidance for long-term management of cancer subjects with VTE is provided by Lyman, et al.[1]
Study Duration:	The expected study duration is approximately 30 months from the time the first subject is enrolled (July 2015) to the time of the last subject's last follow-up visit.
Study Sites and Location:	Approximately 140 study sites in North America, Europe, and Australia/New Zealand are planned to enroll subjects in this study.
Planned Sample Size:	Assuming a hazard ratio of 1, a total of 191 overall primary events is projected to accrue in the modified intention-to-treat (mITT) analysis set which will ensure at least 80% power for the primary analysis at a non- inferiority margin for the hazard ratio of 1.5 and a Type I error of 0.05 (two-sided).

	Assuming a primary combined outcome rate (recurrent VTE or major bleed) of 20.0%, a total of 1000 subjects are expected to be randomized to study treatment in order to accrue 191 overall primary events in the mITT analysis.
Subject Eligibility Criteria:	Adult male or female subjects who present with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin) for whom long-term treatment with LMWH is indicated, are eligible to participate in this study. Key eligibility criteria include: <u>Inclusion Criteria:</u> 1. Male or female subjects with age ≥ 18 years or the otherwise legal lower age according to the country of residence; 2. Confirmed symptomatic or unsuspected lower extremity proximal DVT (ie, popliteal, femoral, iliac or inferior vena cava vein thrombosis), or confirmed symptomatic PE, or unsuspected PE of a segmental or larger pulmonary artery; 3. Cancer, other than basal-cell or squamous-cell carcinoma of the skin. Cancer should be active (see Section 6.1) or diagnosed within 2 years prior to randomization. The diagnosis/history of cancer must be objectively documented; 4. Intention for long-term treatment (at least 6 months) with parenteral LMWH; 5. Able to provide written informed consent. <u>Exclusion Criteria:</u> 1. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of DVT and/or PE; 2. More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, unfractionated heparin, and fondaparinux per local labeling), oral direct anticoagulants or vitamin K antagonist (VKA) prior to randomization to treat the current (index) episode; 3. Treatment with therapeutic doses of an anticoagulant including dalteparin for an indication

other than VTE prior to randomization;

4. Active bleeding or any contraindication for treatment with LMWH/dalteparin or edoxaban;
5. An Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or 4 at the time of randomization (see Appendix 17.6);
6. Calculated creatinine clearance (CrCL) < 30 mL/min;
7. History of heparin associated thrombocytopenia;
8. Acute hepatitis, chronic active hepatitis, liver cirrhosis;
9. Hepatocellular injury with concurrent transaminase (alanine transaminase [ALT]/aspartate transaminase [AST] > 3 x upper limit of normal [ULN]) and bilirubin (> 2 x ULN) elevations in the absence of a clinical explanation;
10. Life expectancy < 3 months;
11. Platelet count < 50,000/mL;
12. Uncontrolled hypertension as judged by the Investigator (eg, systolic blood pressure > 170 mmHg or diastolic blood pressure > 100 mmHg despite antihypertensive treatment);
13. Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding;
14. Chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors for ≥ 4 days/week anticipated to continue during the study;
15. Treatment with aspirin in a dosage of more than 100 mg/per day or dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or intravenous antiplatelet drug) anticipated to continue during the study;
16. Treatment with the P-gp inhibitors ritonavir, nelfinavir, indinavir, or saquinavir anticipated to continue during the study;

	17. Systemic use of the P-gp inhibitors ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin at the time of randomization; subsequent use is permitted (with appropriate dose reduction of edoxaban see Appendix 17.3.7); 18. Subjects with any condition that as judged by the Investigator would place the subject at increased risk of harm if he/she participated in the study.
Dosage Form, Dose and Route of Administration:	Edoxaban (30 mg) will be supplied by the Sponsor as yellow film-coated tablets and administered per oral (PO). LMWH for the edoxaban lead-in will be as prescribed by the Principal Investigator (see Study Design, above). Dalteparin will be supplied by the Sponsor as single-use pre-filled syringes and administered by SC injection.
Study Outcomes:	The primary study outcome is the composite of recurrent VTE, and major bleeding. Recurrent VTE is either: • symptomatic confirmed (new) DVT or (new) PE; • unsuspected (new) proximal DVT of the legs or unsuspected (new) PE located in segmental or more proximal arteries: – Unsuspected DVT or PE are thrombi that are detected during imaging testing performed for other reasons (eg, computed tomography (CT) for cancer staging) and not for suspicion of DVT or PE. • fatal PE (including unexplained death for which PE cannot be ruled out). Secondary Outcomes: • Recurrent VTE; • Major bleeding; • CRNM bleeding; • Major + CRNM bleeding; • All bleeding; • Event-free survival, defined as the proportion of

subjects over time free of recurrent VTE, major bleeding events, and death;

- VTE-related death;
- Mortality from all causes;
- Recurrent DVT;
- Recurrent PE;
- Healthcare resource utilization for potential recurrent VTE and bleed events.

Other outcomes include:

- Cardiovascular events (MI, stroke, SEE [see Appendix 17.5.1]);
- Thrombotic events at other locations (see Appendix 17.5.2);
- Reason for permanent early discontinuation of study drug.

Statistical Analyses:

Analysis of the Primary Study Outcome

The primary analysis will be based on the mITT Analysis Set (which includes all randomized subjects who receive at least 1 dose of study drug) using all primary outcome events (ie, recurrent VTE or major bleeding) occurring from randomization through the end of the 12 month study period or up to the global EOT visit when the study has been stopped, regardless of whether the subject is taking study drug. In this analysis, the time to the first event of the composite outcome will be analyzed using a Cox's proportional hazards model including treatment and the stratification factors as covariates. The LMWH/edoxaban to comparator hazard ratio will be computed along with a 95% confidence interval [CI] (two-sided) based on this model. The LMWH/edoxaban will be considered non-inferior to the comparator if the upper limit of the CI is < 1.5.

The following sensitivity analyses will be performed for the Primary Outcome:

- On-Treatment events based on the per-protocol (PP) Analysis Set will be analyzed using the counting process approach of the Cox proportional hazards regression model including treatment group, and the stratification factors as

covariates. An On-Treatment event is defined as the event occurring during the time period the subject is taking study drug up to 3 days after their last dose for that time period. Only events occurring prior to or on Day 365 will be included into this analysis. Subjects who do not experience an On-Treatment event will be censored at Day 365, or the time study drug is permanently discontinued plus 3 days or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global end of treatment, whichever comes first.

- Events occurring during the first 6 months (180 days) based on the mITT Analysis Set will be analyzed using the same statistical model as the primary analysis of the primary outcome. The time to event is defined as the time (days) from the randomization to the first event during the first 6 months after randomization. Subjects who do not experience an event until Day 180 will be censored at Day 180, or the time study drug is permanently discontinued or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, whichever comes first.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phoshatase
ALT	Alanine transaminase
ANA	Antinuclear antibody
ARO	Academic Research Organization
AST	Aspartate transaminase
BP	Blood pressure
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence interval
CMV	Cytomegalovirus
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CrCL	Creatinine clearance
CRF	Case Report Form
CRNM	Clinically relevant non-major
CRO	Contract Research Organization
CT	Computerized tomography
CTPA	Computerized tomographic pulmonary angiography
CUS	Compression ultrasonography
CVC	Central venous cathether
DMC	Data Monitoring Committee
DTE	Data-driven Trial Execution
DOAC	Direct oral anticoagulant
DTE	Data-driven Trial Execution
DU-176b	Edoxaban tosylate
DVT	Deep vein thrombosis
EBV	Epstein Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Definition
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
EIU	Exposure In Utero
EOT	End of trial
EU	European Union
FDA	Food and Drug Administration
FXa	Factor Xa
GCP	Good Clinical Practice (refers to ICH and CFR)
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITREAS	International Trial Expertise Advisory and Services
IV	Intravenous
IVC	Inferior vena cava
IXRS	Interactive web/voice response System
LFT	Liver function test
LMWH	Low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified intention-to-treat
NSAIDs	Non-steroidal anti-inflammatory drugs
NVAF	Non-valvular atrial fibrillation
PCC	Prothrombin complex concentrate
PD	Pharmacodynamic
PE	Pulmonary embolism

Abbreviation	Definition
PI	Principal Investigator
PK	Pharmacokinetic
PO	Per oral
PP	Per-protocol
PROBE	Prospective, randomized, open-label, blind-evaluator (study design)
QD	Once daily
QOL	Quality of life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SC	Subcutaneous
SDR	Source data review
SDV	Source data verification
SEE	Systemic embolic event
SMCC	Steering Management Coordinating Committee
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
SVT	Splanchnic vein thrombosis
TEAE	Treatment-emergent adverse events
UFH	Unfractionated heparin
ULN	Upper limit of normal
US	United States
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
V/Q scan	Ventilation perfusion scan
WBC	White blood cell
WHODRUG	World Health Organization Drug Reference

1. INTRODUCTION AND BACKGROUND INFORMATION

Venous thromboembolism (VTE) is a common and clinically important disease in cancer patients and current standard treatment consists of long-term low-molecular weight heparin (LMWH).[1,2,3,4] Although subcutaneous (SC) injections with LMWH are effective they are often difficult to tolerate and inconvenient for long-term use by cancer patients. Therefore, if oral medications, such as the current direct oral anticoagulants (DOACs) are effective and safe without the need for SC punctures, they are potentially an attractive alternative in this population. The Hokusai VTE study has shown that edoxaban, an oral direct Factor Xa (FXa) inhibitor, was effective and safe in the treatment of VTE.[5] In a subgroup analysis among 771 cancer patient randomized to the Hokusai VTE study, edoxaban was non-inferior in terms of efficacy and associated with a relative risk reduction of 19% in clinically relevant bleeding compared to warfarin.[6] In view of these results, a clinical study with edoxaban versus LMWH in cancer-associated VTE is proposed.

1.1. Data Summary

The efficacy and safety of edoxaban for the treatment of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), and the prevention of recurrent VTE was demonstrated in the Phase 3 Hokusai VTE study. A large pivotal Phase 3 study in non-valvular atrial fibrillation (NVAF) (ENGAGE AF-TIMI 48) has also been completed and provides important information regarding the safety of long-term edoxaban treatment. 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	Treatment Groups	Number of Subjects	Median Duration of Treatment	Primary Efficacy Endpoint	Primary Efficacy Outcome (Edoxaban vs Warfarin	Primary Safety Endpoint	Primary Safety Outcome (Edoxaban vs Warfarin)
Hokusai VTE (acute VTE)	Edoxaban 60 mg	4118	0.7 years	Recurrent VTE	HR (95% CI) 0.89 (0.703, 1.128)	Major + CRNM Bleeding	HR (95% CI) 0.81 (0.705, 0.936)
	Warfarin	4122					
ENGAGE AF-TIMI 48 (NVAF)	Edoxaban 60 mg	7012	2.5 years	Stroke and SEE	HR (95% CI) 0.79 (0.63, 0.99)	Major Bleeding	HR (95% CI) 0.80 (0.71, 0.91)
	Edoxaban 30 mg	7002					
	Warfarin	7012					

VTE – venous thromboembolism; HR – Hazard Ratio; CI – confidence interval; CRNM – clinically relevant non-major; NVAF – non-valvular atrial fibrillation; SEE – systemic embolic event

Other completed studies include Phase 1 clinical pharmacology studies, Phase 2 dose-ranging studies in subjects with NVAF and subjects undergoing lower-extremity orthopedic surgery, and Phase 3 studies in subjects undergoing lower-extremity orthopedic surgery. In the edoxaban program, a combined total of 18,132 subjects were

treated with edoxaban (7002 with edoxaban 30 mg and 11,130 with edoxaban 60 mg) encompassing over a total exposure of > 34,048 subjects years for edoxaban.[7]

1.1.1. Investigational Product(s)

1.1.1.1. Name

Name of Investigational Product: Edoxaban tosylate (DU-176b)

Edoxaban (INN), anhydrous free base (DU-176)

Active Ingredient: *N*-(5-Chloropyridin-2-yl)-*N*□-[(1*S*,2*R*,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

1.1.1.2. Description

Edoxaban tosylate is an antithrombotic agent, an orally active, selective, direct, and reversible inhibitor of 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. Nonclinical Studies

In nonclinical studies, edoxaban showed excellent potential as an antithrombotic agent. Nonclinical data indicate no evidence of liver function abnormalities in study animals exposed to edoxaban. Additional details are available in edoxaban Investigators' Brochure.[7]

1.1.1.4. Clinical Experience

The global clinical experience with edoxaban includes 43 completed Phase 1 studies, 12 completed Phase 2 studies and 8 completed Phase 3 studies.

Edoxaban has been evaluated in the treatment of VTE in a large pivotal Phase 3 study, the Hokusai VTE study.[5] In this study, 8292 patients were enrolled: 4921 with DVT and 3319 with PE. Patients were randomized to an initial course of LMWH followed by edoxaban or LMWH/warfarin followed by warfarin alone. The primary efficacy analysis of non-inferiority versus the current standard of care (ie, heparin overlapped with warfarin until the international normalized ratio (INR) reaches ≥ 2.0) was demonstrated with a high degree of confidence (hazard ratio [HR]: 0.89; 95% confidence interval [CI]: 0.703, 1.128; p<0.0001). The efficacy was consistent across analysis populations, individual components of the primary endpoint and subgroups of subjects including older individuals, those with renal impairment and subjects with lower body weight. For the primary safety outcome (adjudicated major/clinically relevant non-major (CRNM) bleeding, Safety Analysis Set, On-Treatment Study Period), edoxaban was superior to

warfarin (HR: 0.81; 95% CI: 0.71, 0.94; p=0.0040) for a relative risk reduction of 19%. The benefit was most apparent for more serious bleeding including intracerebral hemorrhage. There was an increase in gastrointestinal (GI) bleeding, in line with other FXa inhibitors.[8] There was also an increase in vaginal bleeding, where the majority of cases were menses-related, but few cases were serious or led to discontinuation of treatment.

It was concluded that once daily edoxaban after heparin was equally efficacious and caused significantly less bleeding compared with high-quality standard therapy with warfarin in a broad spectrum of VTE patients, including those with severe PE.

Additional details are available in the edoxaban Investigators' Brochure.[7]

1.2. Study Rationale

Venous thromboembolism (comprising DVT and PE) is a serious and frequently occurring comorbidity in cancer patients. It is the second most common cause of death in these patients[9] and compared with healthy persons cancer patients have a 4- to 7-fold increased risk for developing VTE.[10,11] The association between thrombotic disease and cancer can be explained by pathophysiological mechanisms, while chemotherapy and central venous catheters (CVCs) often used in this population further increase the risk of VTE.

In addition to a higher risk for developing VTE, patients with a malignancy when treated with anticoagulants also have an increased risk of bleeding, with major bleeding rates that are in the same range as the rate of recurrent VTE (ie, 8% - 12% per year as shown in contemporary studies).[12,13,14]

Given these findings, clinical studies evaluating effective and safe VTE treatment are considered a priority for cancer patients. Since the principal problem in cancer patients with VTE is the underlying cancer, VTE management should preferably not interfere with the cancer therapy and have minimal impact on the patient's already compromised quality of life (QOL). In this respect, VTE treatment in cancer patients is more challenging and different than VTE treatment in non-cancer patients. Current standard therapy for cancer-associated VTE is daily SC injected LMWH-dalteparin for at least 6 months.[1,2,3,4] Although SC injections are effective they are often difficult to tolerate and inconvenient for long-term use by cancer patients. Therefore, if oral medications such as the current direct oral anticoagulants are effective and safe without the need for SC punctures then they are potentially an attractive alternative for patients with cancer and VTE. The Hokusai VTE study has shown that edoxaban, an oral direct FXa inhibitor (DOAC), was effective and safe in treatment of venous thromboembolism.[5] Additionally, among 771 patients with cancer randomized in the study, the recurrence rate over the 12-month study period in the edoxaban group was 3.7% compared with 7.1% in the warfarin group (HR: 0.53; 95% CI: 0.28, 1.00). In these same patients, the clinically significant bleeding rates were 12.4% versus 18.8% (HR: 0.64; 95% CI: 0.45, 0.92) in the edoxaban and warfarin treatment groups, respectively.[6] Interestingly, in the subgroup of patients classified by the treating physician as having cancer active at entry in the study (n=208), the risk of VTE recurrence was 3.7% in the edoxaban group and 7.1% in the warfarin group (HR, 0.55; 95% CI, 0.16, 1.85), showing virtually identical

results between patients with a history of cancer and the subset of those considered by the physician to have "active" cancer. This novel observation illustrates that the risk with respect to recurrent VTE is more the history of cancer than the more narrow definition of cancer that is "active." This conclusion was reached also in another recent study in a subgroup of cancer patients with VTE.[15]

In view of these results, a comparative clinical study between standard treatment consisting of long-term SC LMWH-dalteparin and the new oral direct FXa inhibitor, edoxaban, is proposed.

In a clinical study evaluating new anticoagulant therapy in the cancer patient population several design aspects require consideration.

- Both recurrent VTE and major bleeding are potential life-threatening complications occurring at a comparable rate and with a significant and similar impact on the patient's clinical status. The VTE-treatment should therefore aim to prevent both recurrent VTE and major bleed and in a study evaluating a new treatment option and the 2 outcomes will need to be equally considered. Therefore, in this novel design it is proposed that the primary outcome of the study will be a combined outcome consisting of recurrent VTE and major bleeding.
- In cancer patients, VTE-symptoms often are not obvious and erroneously attributed to the cancer or its treatment. This unsuspected VTE occurs frequently[16,17,18] and the prognosis of these unexpected VTEs in terms of recurrent VTE and mortality are similar to those with symptomatic disease.[1,19,20,21,22] As a consequence, current guidelines advise a similar treatment strategy for unsuspected PE and DVT as for clinically apparent VTE.[1] Therefore, unsuspected PE and DVT will be considered as an inclusion criterion and also as a component of the primary outcome.
- In non-cancer patients the duration of VTE-treatment is at least 3 months and prolonged up to 12 months or indefinitely depending on the clinical judgment balancing risk and benefit. In cancer patients the recommended treatment duration is at least 6 months. Consistent with guideline recommendations prolonging treatment needs to be strongly considered especially in patients in whom cancer is still present.[1,2,3] However, after 6 months physicians are faced with a dilemma since data from studies beyond 6 months are absent.[1,2,3] In evaluating a new anticoagulant treatment it is desirable to document the effects of treatment over a longer period of time. Therefore, the intent in the present study is to treat all subjects for 12 months, and to follow all subjects for 12 months after randomization whether or not they complete 12 months of treatment. This is important because bleeding, including CRNM bleeding events, may lead to discontinuation or interruption of anticoagulant therapy, which then increases the risk of subsequent recurrent VTE events, with such events not captured using traditional On-Treatment analyses.

1.3. Risks and Benefits for Study Subjects

Edoxaban is a selective FXa inhibitor with rapid onset of action and predictable antithrombotic properties. Edoxaban appears to be well tolerated up to a dose of 90 mg QD, with expected transient and manageable bleeding adverse events (AEs) and transient and reversible liver enzyme and bilirubin elevations.

In the edoxaban program, a combined total of 18,132 subjects were treated with edoxaban (7002 with edoxaban 30 mg and 11,130 with edoxaban 60 mg) encompassing over a total exposure of > 34,048 subjects years for edoxaban.[7] This exceptionally large database allowed the overall safety of edoxaban to be adequately characterized in terms of adverse reactions with rare frequency and those occurring after a long latency period. The program also conducted a large number of specific studies to allow characterization of the pharmacokinetic (PK) and safety profile of edoxaban in subjects with hepatic dysfunction, severe renal impairment, and concomitant medications. These specific studies together with the large clinical database allowed for the safety of edoxaban to be assessed in a large number of subject subgroups of intrinsic and extrinsic factors. Edoxaban demonstrated a consistent safety profile across subgroups. An effective oral and parenteral transition scheme from edoxaban to other anticoagulants has also been demonstrated.

The completed Phase 3 clinical trials in AF and VTE have demonstrated efficacy and safety of edoxaban 60-mg dose (with a 30-mg dose reduction in subjects with 1 or more of the following: moderate to severe renal impairment, weight ≤ 60 kg, or concomitant use of specified P-gp inhibitors) in the prevention of stroke and systemic embolism in adult subjects with NVAF and in the treatment of VTE including DVT and PE, and prevention of recurrent VTE.

For VTE in particular, the primary efficacy analysis of non-inferiority versus the current standard of care (ie, heparin overlapped to warfarin until the INR reaches ≥2.0) was demonstrated with a high degree of confidence. In the primary efficacy modified intention-to-treat (mITT) overall analysis, the edoxaban regimen demonstrated non-inferiority versus warfarin (HR: 0.89; 95% CI: 0.703, 1.128; p<0.0001). The efficacy was consistent across analysis populations, individual components of the primary endpoints and subgroups of subjects including older individuals, those with renal impairment, and lighter subjects.

Edoxaban 60 mg showed a clear benefit in terms of reduced bleeding when compared with well-controlled warfarin treatment. In the Hokusai VTE study, the primary safety endpoint (adjudicated major/CRNM bleeding, Safety Analysis Set, On-Treatment Study Period), edoxaban was superior to warfarin (HR: 0.81; 95% CI: 0.71, 0.94; p=0.0040) for a relative risk reduction of 19%. The benefit was most apparent for more serious bleeding including ICH, and intra-articular and intra-ocular bleeds. There was an edoxaban associated increase in GI bleeding, in line with other FXa inhibitors. There was also an increase in vaginal bleeding, where the majority of cases were menses-related, but few cases were serious or led to discontinuation of treatment.

Bringing together quantitatively the benefits and risks as a net clinical outcome, Table 1.2 summarizes the benefit-risk outcomes. For each indication, the net clinical outcome covers the principal efficacy and safety outcomes, and includes all-cause mortality.

Table 1.2: Quantitative Benefit Risk

Composite Endpoint	HR (95% CI) for Edoxaban 60 mg versus Warfarin
NVAF: Net Clinical Outcome mITT, Overall	0.89 (0.83 to 0.96)
VTE: Net Clinical Outcome PP, On-Treatment	0.87 (0.70 to 1.10)

HR – Hazard Ratio; CI – confidence interval; NVAF – non-valvular atrial fibrillation; mITT – modified intention-to-treat; VTE – venous thromboembolism; PP – per protocol

For NVAF, net clinical outcome is a composite of stroke, systemic embolic event, major bleeding, and all-cause mortality.

For VTE, net clinical outcome is a composite of symptomatic recurrent deep vein thrombosis, non-fatal symptomatic recurrent pulmonary embolism, fatal pulmonary embolism, and major bleeding, and all-cause mortality.

Overall, edoxaban has an adequately characterized positive benefit-risk ratio in large and representative populations globally in patients with NVAF and VTE, demonstrating efficacy in the overall populations and subgroups (with dose reduction as required) in conjunction with a favorable bleed profile as well as demonstrating its effectiveness in a dose-dependent manner for VTE prevention after orthopedic surgery such as hip or knee replacement. Additional advantages of edoxaban are its once daily (QD) dosing, dose-reduction strategies to minimize the risk of bleeding with preserved efficacy and no necessity for constant monitoring of therapy.

Dalteparin is the only licensed anticoagulant for the extended treatment and prevention of recurrence of VTE in cancer patients and thus is considered the “gold” standard treatment. Six months of dalteparin was found to be more effective than, and as safe as, vitamin K antagonists [VKAs] (ie, warfarin/coumarin) for patients with cancer and acute VTE, without significantly increasing the risk of major bleeding. The authors concluded that “longer term” dalteparin is safe in cancer patients.[23]

References and information on dalteparin (Fragmin®) is available in the Summary of product Characteristics/Product Monograph and the package inserts.[24]

Complete prescribing information for dalteparin can be found in Appendix 17.1.1.

1.4. Population, Route, Dosage, Dosage Regimen, Treatment Period

Adult subjects who present with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin) for whom long-term treatment with LMWH is intended are eligible to participate in this study. Section 4 lists all eligibility requirements necessary to qualify for the study.

Eligible subjects will be stratified by 1) bleeding risk, and 2) the need for dose adjustment, and then randomized to receive either LMWH/edoxaban or dalteparin (see full details below; Section 3 provides complete treatment details).

- Edoxaban group: Therapeutic doses of LMWH (SC) for at least 5 days will be administered; this 5 day period may include the pre-randomization LMWH treatment (if applicable). The choice of parenteral LMWH is up to the treating physician. Thereafter, edoxaban will be started orally at 60 mg QD (2 × 30 mg tablets; 30 mg QD for subjects requiring dose adjustment) for the remainder of the treatment period.
- Dalteparin group: After randomization, dalteparin will be administered at a dose of 200 IU/kg SC (maximum daily dose 18,000 IU) for 30 days. The 30 day period may include the pre-randomization anticoagulant treatment if dalteparin was used in therapeutic doses. Thereafter (approximately Day 31 forward), dalteparin will be administered at a dose of 150 IU/kg SC (~ 75% - 83% of the initial dose) for the remainder of the treatment period.

1.5. 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 Conference on Harmonisation (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) and/or
- European Commission Directive (2005/28/EC Apr 2005) and/or
- Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, Parts 11, 50, 54, 56 and 312 as appropriate and/or
- Other applicable local regulations.

1.5.1. Subject Confidentiality

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

For European Union (EU) sites, 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/electronic CRF [eCRF]) or other documents submitted to the Sponsor and/or its designated representatives, subjects should be identified by a unique subject identifier as designated by the sponsor. Documents that are not for submission to Sponsor and/or it's designated representatives (eg, signed Informed Consent Forms [ICFs]) should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/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) or Institutional Review Board (IRB) direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform

the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

1.5.2. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject or legally acceptable representative 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 (see Section 6.1 Study Qualification). A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The written ICF should be prepared in the local language(s) of the potential subject population.

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

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the subject or a legally acceptable representative, and by the appropriate qualified person who conducted the informed consent discussion (not necessarily the Investigator but delegated by the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legal representative. The date that informed consent was given should be recorded on the CRF.

If the subject or legally acceptable representative cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject or the legally acceptable representative has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject or the legally acceptable representative.

Suggested model text for the ICF for the study and any applicable subparts (genomic, pharmacokinetic, etc) are provided in the Sponsor ICF template for the Investigator to prepare the documents to be used at his or her site. Updates to applicable forms will be communicated via letter from the Clinical Study Manager.

This study will be conducted in the United States (US), therefore, additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

1.5.3. Regulatory Compliance

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

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the Statistical Analysis Plan (SAP).

The Investigator must submit and, where necessary, obtain approval from the IEC or IRB and/or Sponsor for all subsequent protocol amendments and changes to the informed consent document or changes of the site, facilities or personnel. The Investigator should notify the IEC or IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Sponsor/contract research organization (CRO), in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will ensure 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 Objective

The primary objective is to demonstrate the non-inferiority of edoxaban (preceded by a short course of LMWH) compared with dalteparin for the prevention of the combined outcome of recurrent VTE or major bleeding in subjects with VTE associated with cancer during a 12-month study period. If non-inferiority is established, LMWH/edoxaban will be compared with dalteparin for superiority.

2.1.2. Secondary Objectives

The secondary objectives are to compare LMWH/edoxaban with dalteparin with regards to rates of:

1. Recurrent VTE;
2. Major bleeding;
3. CRNM bleeding;
4. Major + CRNM bleeding;
5. All bleeding;
6. Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
7. VTE-related death;
8. Mortality from all causes;
9. Recurrent DVT;
10. Recurrent PE;
11. Healthcare resource utilization for potential recurrent VTE and bleed events.

2.1.3. Exploratory Objectives

Exploratory objectives include comparing LMWH/edoxaban with dalteparin with regards to:

1. Cardiovascular events (myocardial infarction (MI), stroke, SEE [see Appendix 17.5.1]);
2. Thrombotic events at other locations (see Appendix 17.5.2);
3. Reason for permanent early discontinuation of study drug.

2.2. Study Hypothesis

Edoxaban will be non-inferior to dalteparin with respect to the occurrence of recurrent VTE or major bleeding in the treatment of VTE associated with cancer.

The study treatment (edoxaban) will be considered non-inferior to the standard therapy (dalteparin) if the upper limit of the two-sided 95% CI for the hazard ratio (edoxaban/standard therapy) is < 1.5.

3. STUDY DESIGN

3.1. Overall Plan

3.1.1. Study Type

This is a multinational, prospective, randomized, open-label, blind-evaluator (PROBE), non-inferiority study comparing edoxaban with dalteparin for prevention of the combined outcome of recurrent VTE or major bleeding in patients with VTE associated with cancer. Adult subjects with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin; cancer should be active (see Section 6.1) or diagnosed within the previous 2 years), and who present with confirmed acute symptomatic or unsuspected lower extremity proximal DVT, confirmed symptomatic PE, or unsuspected PE in a segmental or larger pulmonary artery for whom long-term treatment (at least 6 months) with LMWH is indicated are eligible to participate in this study. One thousand subjects (1000) will be equally randomized to 1 of the 2 treatment groups.

After a subject's eligibility is confirmed, the subject will be stratified by 1) bleeding risk, and 2) the need for dose adjustment, and then randomly assigned via interactive voice/web response system (IXRS) in a 1:1 ratio to treatment with either LMWH/edoxaban or dalteparin (see Section 5.1.1 for complete details).

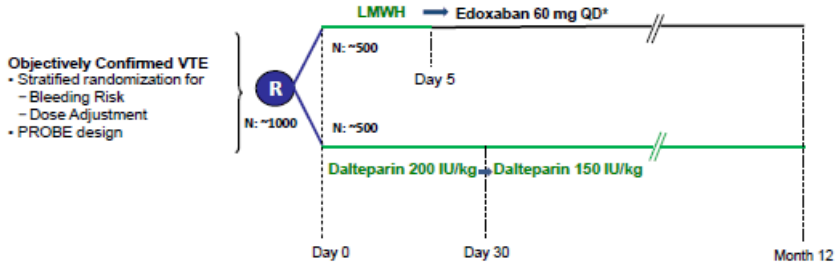
After randomization subjects will be assessed at Month 1, Month 3, and then quarterly thereafter for up to 12 months until they complete the study.

Approximately 140 study sites in North America, Europe, and Australia/New Zealand are planned to enroll subjects in this study.

3.1.2. Treatment Groups and Dosing

Figure 3.1 depicts the study design and treatment plan. The detailed Schedule of Events is provided in Appendix 17.7 and the protocol-required study procedures are provided in Section 6.

Figure 3.1: Study Design



Eligible subjects will be stratified by 1) bleeding risk, and 2) the need for dose adjustment:

1. Bleeding risk (assessed at time of randomization)
   - surgery within 2 weeks prior to randomization
   - use of antiplatelet agents (eg, aspirin ≤ 100 mg/day) that will continue during the study
   - brain tumor or brain metastases present at the time of randomization
   - metastatic disease present at the time of randomization
   - regionally advanced cancer present at the time of randomization
   - gastrointestinal cancer at randomization or diagnosed within a 6-month period prior to randomization
   - urothelial cancer at randomization or diagnosed within a 6-month period prior to randomization
   - Avastin (bevacizumab) use at randomization or given within the 6-week period prior to randomization
2. The need for dose adjustment
   - body weight ≤ 60 kg, or
   - creatinine clearance (CrCL) between 30 and 50 mL/min inclusive
   - concomitant use of P-gp inhibitors

After stratification, subjects will be assigned randomly via IXRS in a 1:1 ratio to 1 of the 2 following treatment groups:

- **LMWH/Edoxaban group**: Therapeutic doses of LMWH (SC) will be administered for at least 5 days; this 5-day period may include the pre-randomization LMWH (if applicable). The choice of this parenteral LMWH

is up to the treating physician. Thereafter, edoxaban will be started orally at 60 mg QD (2 × 30 mg tablets; 30 mg QD for subjects requiring dose adjustment) for the remainder of the treatment period.

The first dose of edoxaban should be taken:

- 12 (±3) hours after the last injection of the initial LMWH if this was a twice daily regimen,
- 24 (±3) hours after the last injection of the initial LMWH if this was a once daily regimen.

The edoxaban daily dose should be decreased to 30 mg QD for:

- body weight ≤ 60 kg; or
- creatinine clearance [CrCL] between 30 and 50 mL/min inclusive;
- concomitant use of P-gp inhibitors (eg, hormonal agents: tamoxifen, enzalutamide, abiraterone).

Dose reduction of edoxaban to 30 mg QD is intended only during concomitant use of P-gp inhibitors. When use of these inhibitors is discontinued/intermittent (eg, between chemotherapy cycles) the full 60 mg edoxaban dose should be used.

After randomization, if the subject's CrCL becomes ≤ 50 mL/min and ≥ 30 mL/min and the decrease in CrCL is > 20% from the subject's baseline CrCL value, repeat the measurement preferably within 1 week. If the repeat measurement confirms this decrease, the edoxaban dosage regimen will be reduced permanently, even if the subject subsequently experiences improved CrCL to > 50 mL/min at a later measurement.

After randomization, if the subject's body weight drops to ≤ 60 kg (confirmed by repeat measurement at least 1 week apart) and the body weight change is > 10% of the subject's baseline body weight, the edoxaban dosage regimen will be reduced permanently, even if the subject subsequently re-gains weight to > 60 kg.

More details are provided in Appendix 17.3.7.

- **Dalteparin group**: After randomization, dalteparin will be administered at a dose of 200 IU/kg SC (maximum daily dose 18,000 IU) for 30 days. The 30 day period may include the pre-randomization anticoagulant treatment if dalteparin was used in therapeutic doses. Thereafter (approximately Day 31 forward), dalteparin will be administered at a dose of 150 IU/kg SC (~ 75% - 83% of the initial dose) for the remainder of the treatment period.

Dalteparin doses by weight and precautions for dose modifications are listed in Appendix 17.4.

3.1.2.1. Treatment Duration

The intention is to treat patients for 12 months with the allocated study treatment.

Continuation of anticoagulant treatment beyond 6 months will be based on the risk-benefit evaluation by the treating physician.

Continue anticoagulation treatment if the benefit of doing so outweighs the risk and/or cancer is still "active". In this case ongoing anticoagulation with the allocated treatment regimen is preferred (if this is considered appropriate by the Investigator). If however the Investigator decides to switch to another treatment regimen (eg, in the dalteparin arm the decision can be made to stop the parenteral administration and switch to oral therapy), it is recommended to switch to VKA and strongly discouraged to switch to a DOAC.

Note: All subjects, including those in whom study medication is stopped or those who switch to VKA, will be followed up to 12 months with the following exception:

Once 1000 subjects are randomized in the study, a global end-of-treatment (EOT) date will be established that ensures a minimum of 6 months of study treatment and follow-up for the final subject(s) randomized. All subjects will permanently discontinue study treatment on or before the EOT date.

3.1.3. Study Governance

3.1.3.1. Steering Committees

The study oversight will be managed by a Steering Management Coordinating Committee (SMCC) whose members are country coordinators, as well as, non-voting representatives of the Sponsor and Academic Research Organization (ARO). In this study, International Trial Expertise Advisory and Services (ITREAS) will function as the ARO.

An Executive Committee to the SMCC will have a scientific advisory function and will not be involved in operational matters.

Ongoing study oversight and management will be the responsibility of a joint supervisory committee. The members of this committee are the chairman and co-chair of the SMCC and designated representatives from the Sponsor, CRO and ARO.

3.1.3.2. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will monitor safety during the study and give recommendations to the Executive Committee. The DMC will periodically review and examine the safety and efficacy data (mortality and events, bleeding events, serious adverse events [SAEs], systemic embolic event [SEE]) and alert the Chairman of the Executive Committee in case of any clinically concerning safety issues.

3.1.3.3. Clinical Events Committee

An independent Clinical Events Committee (CEC) will be established to objectively adjudicate and categorize the presenting index diagnosis, VTE outcomes, cardiovascular events, bleeding events, selected hepatic events, and death. Adjudicators will be blinded as to subject treatment allocation.

3.1.4. Study Outcomes

3.1.4.1. Primary Outcome

The primary outcome is the composite of recurrent VTE, and major bleeding.

All suspected recurrent VTE and bleeding events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

See Section 7.1 for complete details of the primary outcome.

3.1.4.2. Secondary Outcomes

Secondary outcomes include:

- Recurrent VTE;
- Major bleeding;
- CRNM bleeding;
- Major + CRNM bleeding;
- All bleeding;
- Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE -related death;
- Mortality from all causes;
- Recurrent DVT;
- Recurrent PE;
- Healthcare resource utilization for potential recurrent VTE and bleed events.

All suspected VTE events, deaths, and bleeding events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

3.1.4.3. Other Outcomes

Other outcomes include:

- Cardiovascular events (MI, stroke, SEE[see Appendix 17.5.1]);
- Thrombotic events at other locations (see Appendix 17.5.2);
- Reason for permanent early discontinuation of study drug.

All suspected cardiovascular events and other thrombotic events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

3.2. Selection of Doses

3.2.1. Experimental Treatments

In the current guidelines extended LMWH therapy is the first choice for long-term treatment of VTE in cancer patients.[1, 2, 3] Dalteparin is the only approved anticoagulant specifically indicated for the extended treatment and prevention of recurrent VTE in cancer patients; thus, it is considered the standard of care. The dalteparin regimen to be used in this study is based on the CLOT study which showed that 6 months of dalteparin was more effective than and as safe as VKAs (ie, warfarin/coumarin) for patients with cancer and acute VTE, without significantly increasing the risk of major bleeding.[23]

The edoxaban regimen (60 mg QD with dose reduction for specific risk factors) was selected for this study based on the Hokusai VTE study results. In the Hokusai VTE study, edoxaban produced a 47% relative reduction in risk for recurrent VTE in subjects with a history of cancer compared with warfarin. Additionally, edoxaban resulted in a 36% relative reduction for risk of clinically significant bleeding in these same subjects.[25]

4. STUDY POPULATION

4.1. Enrollment

Subjects must sign and date the ICF provided by the site before any study-specific qualification procedures are performed, except as noted in Section 6.1 Study Qualification/Pre-randomization.

4.1.1. Inclusion Criteria

Adult subjects presenting with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin) for whom long-term treatment with LMWH is intended are eligible to participate in the study.

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

1. Male or female subjects with age ≥ 18 years or the otherwise legal lower age according to the country of residence;
2. Confirmed symptomatic or unsuspected lower extremity proximal DVT (ie, popliteal, femoral, iliac or inferior vena cava (IVC) vein thrombosis), or confirmed symptomatic PE, or unsuspected PE of a segmental or larger pulmonary artery;
3. Cancer (other than basal-cell or squamous-cell carcinoma of the skin), either active or diagnosed within 2 years prior to randomization. [Note: Diagnosis of cancer must be objectively documented];
4. Intention for long-term treatment (at least 6 months) with parenteral LMWH;
5. Able to provide written informed consent.

4.1.2. Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for enrollment:

1. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of DVT and/or PE;
2. More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, unfractionated heparin, and fondaparinux per local labeling), oral direct anticoagulants or VKA prior to randomization to treat the current (index) episode;
3. Treatment with therapeutic doses of an anticoagulant including dalteparin for an indication other than VTE prior to randomization;
4. Active bleeding or any contraindication for treatment with LMWH/dalteparin or edoxaban;
5. An Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or 4 at the time of randomization (Appendix 17.6);

6. Calculated CrCL < 30 mL/min;
7. History of heparin associated thrombocytopenia;
8. Acute hepatitis, chronic active hepatitis, liver cirrhosis;
9. Hepatocelullar injury with concurrent transaminase (ALT/AST > 3 x ULN) and bilirubin (> 2 x ULN) elevations in the absence of a clinical explanation;
10. Life expectancy < 3 months;
11. Platelet count < 50,000/mL;
12. Uncontrolled hypertension as judged by the Investigator (eg, systolic blood pressure (BP) > 170 mmHg or diastolic blood pressure > 100 mmHg despite antihypertensive treatment);
13. Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding;

Note: Childbearing potential without proper contraceptive measures (ie, a method of contraception with a failure rate < 1 % during the course of the study including the observational period). These methods of contraception according to the note for guidance on nonclinical safety studies for the conduct of human trials for pharmaceuticals (CPMP/ICH/286/95, modification) include consistent and correct use of hormone containing implants and injectables, combined oral contraceptives, hormone containing intrauterine devices, surgical sterilization, sexual abstinence, and vasectomy for the male partner).

14. Chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors for ≥ 4 days/week anticipated to continue during the study;
15. Treatment with aspirin in a dosage of more than 100 mg/per day or dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or intravenous [IV] antiplatelet drug) anticipated to continue during the study;
16. Treatment with the P-gp inhibitors ritonavir, nelfinavir, indinavir, or saquinavir anticipated to continue during the study;
17. Systemic use of the P-gp inhibitors ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin at the time of randomization; subsequent use is permitted (with appropriate dose reduction of edoxaban see Appendix 17.3.7);
18. Subjects with any condition that as judged by the Investigator would place the subject at increased risk of harm if he/she participated in the study.

4.2. Removal of Subjects From Therapy

4.2.1. Reasons for Withdrawal/Early Discontinuation

A subject may discontinue or interrupt study drug for a number of reasons including, but not limited to, those listed below:

Permanent Early Discontinuation

- Death;
- Withdraw of consent as defined in Section 4.2.1.2;
- Lost to follow-up as defined in Section 4.2.1.3 (every attempt will be made by the Investigator not to have subjects "lost to follow-up");
- CrCL decrease to < 30 mL/min, confirmed by repeat testing at least 1 week later or need for kidney dialysis;
- Investigator judgment due to:
  - SAE or other safety concern eg,
    - Major life-threatening bleeding
    - Onset clinical jaundice or other overt signs of liver toxicity
  - Unfavorable benefit-to-risk evaluation for continuing anticoagulant treatment
- Subject decision (refusal for intake or administration of study drugs). It is important to distinguish between withdrawal of consent with regards to continuing on study medication but continuing to be followed on study;
- Termination of all or part of the study by the SMCC acting in concert with the Sponsor.

4.2.1.1. Temporary Interruption

Temporary interruptions of initial LMWH, edoxaban and dalteparin for 4 or more consecutive days will be recorded in the eCRF. Potential reasons may include:

- Short-term use of prohibited concomitant medications;
- Surgical procedures;
- Any medical condition where continuing study drug may expose the subject to an increased hazard;
- New onset of elevated liver enzymes in the absence of a known cause:
  - ALT > 8 × ULN or
  - AST or ALT > 5 x ULN for more than two weeks
  - ALT or AST > 3 x ULN, but not reaching the limits in the above criteria, in combination with clinical symptoms suggestive of hepatitis
  - ALT or AST > 3 x ULN with TBL > 2 x ULN

Interruptions for less than 4 consecutive days will not be recorded in the eCRF unless the medication was interrupted due to an adverse event (ie, any interruption in study medication due to an AE must be recorded in the eCRF).

During a study drug interruption or after study drug discontinuation, a subject can be placed on antithrombotic therapy per local guidelines and the Investigator's discretion. It is, however, discouraged to switch to another DOAC. Guidance for switching from edoxaban to other anticoagulants is provided in Appendix 17.2.

Post-randomization changes (other than CrCL decreased to < 30 mL/min or need for kidney dialysis) in health status related to study exclusion criteria should not automatically lead to study drug interruption or discontinuation unless continuing study drug places the subject at undue hazard as determined by the Investigator. Such situations should be handled on a case-by-case basis. It is strongly recommended that the Investigator consults with ITREAS (Medical Support Line: +32 495 54 74 51) if a subject has a post randomization change in health status that is associated with an exclusion criterion.

Also, a decision to stop prematurely the overall recruitment in the study and/or intake of study drug can be taken by the Executive Committee /Sponsor following advice on safety aspects of the study by the DMC. The IECs/IRBs will be informed of this decision. The DMC stopping guidelines will be defined prior to the start of the study. The Sponsor has the right to close this study and the right to close a center, at any time, although this should occur only after consultation between involved parties and the Executive Committee. The IECs/IRBs must be informed. Should the site be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the Sponsor. The Investigator will retain all other documents until notification by Sponsor for destruction

If the subject is withdrawn due to an adverse event, the Investigator will follow the subject until the adverse event has resolved or stabilized.

4.2.1.2. Withdrawal of Consent from Study Participation

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw consent 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.

However, it is important to distinguish between refusal to continue on study medication and continuing to be followed on study versus withdrawal of consent with regards to continuing the study all together (ie, withdrawal of consent with regards to continuing on study medication and any further study follow-up).

Only subjects who refuse all 4 of the following methods of follow-up will be considered to have withdrawn consent from study participation:

- Participation in the trial follow-up visits per protocol, either in clinic or by telephone;
- Contact by trial personnel even if only by telephone (quarterly, bi-annually, annually, End of Treatment visit only);
- Permission for trial personnel to contact an alternative person (eg, family member, spouse, partner, legal representative, physician, the anticoagulation clinic, or another healthcare provider) even if only by telephone;

- Permission for trial personnel to access and review their medical information from alternative sources (eg, doctor's notes, hospital records).

If the subject refuses all 4 of the above methods of follow-up, the Investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. If the subject continues to refuse all potential methods of follow-up, the Investigator will document this as a withdrawal of consent in the medical record.

All subjects should be followed for the full duration of the trial using any or all of the above methods, unless there is written documentation by the Investigator of the subject's withdrawal of consent to ALL of the above methods of follow-up.

If a subject is withdrawn entirely from the study, the IXRS will be called by the site to register the subject as permanently discontinued from the study (and study treatment if not done previously).

The site will complete and report the observations as thoroughly as possible up to the date of consent withdrawal and including the date of the final dose of study drug. The reason(s) for limited follow-up/data collection will be clearly documented in the medical record and eCRF.

Public databases and subject finder services may be used to determine subject status and to locate potential lost to follow-up patients.

4.2.1.3. Subjects Lost to Follow-Up

The Investigator will make every effort not to have any subjects lost to follow-up. If a subject is potentially lost to follow-up (eg, missed study visits, unable to be contacted by phone), the Investigator will make every effort to contact the subject before the subject is declared lost to follow-up. These efforts may include but are not limited to:

- Calling all telephone numbers for the subject and their contacts (including during the evening and on weekends);
- Calling primary care physician, referring specialist and/or other listed physicians for more recent locator information, date of last office visit, or to determine mortality status;
- Sending email and follow with mailing certified letters (return receipt requested) to all known subject addresses and all listed contacts (eg, relatives, friends, neighbors);
- Reviewing subject's records and medical notes for any details of a hospitalization, doctor's visit, or other procedure that may indicate status of subject;
- Using the Internet to search for possible contact information for subject
  - Try reverse directory for phone numbers to get possible addresses
  - Utilize social networking sites (eg, Facebook);

- Checking local, regional, and national public records to locate subject or search for mortality status in accordance with local law;
- Possible home visit.

Once the site has exhausted and documented these actions, the Clinical Research Associate or monitor should be contacted for additional guidance and alternative options. Public databases and subject finder services may be used to determine subject status and to locate potential lost to follow-up patients.

4.2.2. Withdrawal Procedures

4.2.2.1. Follow-Up of Subjects with Study Drug Discontinuations

The Investigator may contact ITREAS (Medical Support Line: +32 495 54 74 51) or email) in case of any questions regarding how to handle a study drug discontinuation or interruption.

All randomized subjects, including those who temporarily interrupted or discontinued study drug, will be followed for a 12-month period after randomization, except when the study is truncated as noted in Section 3.1.2.1.

In case of premature discontinuation of treatment, study outcomes can be collected by telephone contact until 12 months after the first dose of study drug. If the subject has an on-site visit at any time after study drug discontinuation, it is expected that a clinical status will be obtained along with any laboratory assessments deemed appropriate by the Investigator.

If the subject and Investigator agree that study drug can be resumed without increased hazard to the subject, study medication may be resumed at any time, regardless of the duration of study drug interruption.

Any subject who temporarily interrupts or discontinues study drug due to confirmed liver enzyme abnormalities or jaundice in the absence of a known cause (eg, underlying cancer), should have an evaluation to determine the cause of the event. Evaluation may include the following depending on the clinical situation:

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

In the absence of a known cause, follow-up of liver enzymes and bilirubin (total and direct) should be performed on a regular basis until the values are stabilized.

All laboratory results, including local laboratory reference ranges are to be recorded in the eCRF.

If the subject and Investigator agree that study drug can be resumed without increased hazard to the subject, study drug may be resumed at any time, regardless of the duration of study drug interruption.

All clinically significant hepatic enzyme abnormalities and/or hepatic events are to be documented in the eCRF and prompt submission of the adjudication dossier should also occur when indicated/directed (see Section 9.3.1).

5. TREATMENTS ADMINISTERED

5.1. Investigational Products

The Investigator must ensure that the investigational products will be used only in accordance with the protocol.

- Edoxaban (30 mg) will be supplied by the sponsor as yellow film-coated tablets and administered orally (PO).
- LMWH for the edoxaban lead-in will be as prescribed by the Principal Investigator (PI).
- Dalteparin will be supplied by the Sponsor as single-use pre-filled syringes and administered by SC injection.

The Investigator or designee will be responsible for dispensing study drugs.

The Investigators/study coordinators must ensure that the appropriate fields on the label are completed, including subject number and date of dispensing.

Subjects must be supplied with sufficient study drug to last until the next scheduled dispensing visit.

Subjects may take edoxaban with or with or without food, in the AM or PM, but at approximately the same time every day. Dalteparin should also be consistently administered at approximately the same time every day as well.

5.1.1. Method of Assigning Subjects to Treatments and Dispensing of Study Drug

Eligible subjects will be stratified by 1) bleeding risk, and 2) the need for dose adjustment. After confirmation of eligibility, the Investigator will provide the IXRS with the study center number, appropriate demographic information consistent with local regulations, bleeding risk profile, CrCL, body weight category (≤ 60 kg or > 60 kg), and whether the subject's currently using P-gp inhibitors (see Appendix 17.3.7).

The IXRS will assign the unique subject identification number, stratify the subject by bleeding risk and need for dose adjustment, then allocate the treatment group assignment for the subject. A fax or email will be sent by the IXRS to the study site noting the treatment group and dosage strength of the assigned medication. The fax or e-mail will also provide a calendar of subsequent dispensing dates. Study drug will be dispensed at randomization, approximately Day 31, Month 2 then at least once every 3 months (more frequent dispensing of study drug is allowed if necessary), thereafter while the subject remains on treatment.

This study has an open-label, blind-evaluator design with LMWH/edoxaban and dalteparin. The subjects, Investigators, Sponsor, CRO, and ITREAS staff involved in the treatment or clinical evaluation of the subjects will be aware of the treatments received. There will be an independent DMC to monitor the efficacy and safety data on a periodic basis. All study outcome events will be adjudicated by the CEC using blinded evaluators.

The specifications for generation of the randomization schedule will be prepared by the study biostatistician and the CRO in charge of the IXRS. For this study, the randomization schedule refers to a list that includes the randomization number, randomization block number, and treatment.

5.1.2. Method of Assessing Treatment Compliance

Dosing compliance will be assessed by means of edoxaban tablet and dalteparin syringe counts.

5.1.3. Labeling and Packaging

Edoxaban 30 mg tablets for oral use will be supplied by the Sponsor in PVC/foil blister packs.

Dalteparin will be supplied in pre-filled syringes.

Drug labeling will be according to national law and Good Manufacturing Practice (GMP) ruling Annex 13.19.

5.1.4. Storage

5.1.4.1. Edoxaban

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

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

5.1.4.2. Dalteparin

Dalteparin must be stored at controlled room temperature below 25°C (77°F).

5.1.5. Drug Accountability

The IXRS will contain a Drug Accountability Module for any medications provided by the Sponsor (eg, edoxaban, dalteparin). The Investigator or designee will enter the required information (see IXRS user manual) in the IXRS drug accountability module. In addition, the Investigator or designee shall contact Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the investigational products. The record must be kept current and should contain, the dates and quantities of drug received, subject's (identification number and/or initials or supply number as applicable), for whom the investigational product was dispensed, the date and quantity of investigational product dispensed and remaining, if from individual subject drug units as well as the initials of the dispenser.

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

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

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

5.2. Concomitant Medications

Pre-specified medications that the subject has taken within 30 days before randomization or during the study will be recorded in the "targeted concomitant medications" eCRF. These pre-specified medications taken by the subjects upon entry to the study or at any time during the study are regarded as targeted concomitant medications and must be documented on the appropriate pages of the eCRF. If the subject has an endpoint event or an SAE, then information on targeted and non-targeted concomitant medications taken within the past 30 days must be documented on the appropriate eCRF pages. Concomitant therapy will be captured until the subjects completes the 12-month study period.

A list of specifically excluded medications is provided in Appendix 17.3. The list reflects the list at the beginning of the study. If there are changes to this list during the study, the changes will not be considered a protocol amendment but updated information. It is strongly encouraged to restrict the dose of aspirin (if indicated) to ≤ 100 mg daily, although higher doses are permitted for strong clinical indication (eg, development of an acute MI).

5.3. Therapeutic Management of Subjects in Emergency Situations

5.3.1. Bleeding

There is no specific antidote to reverse the effect of edoxaban. The following steps are recommended for subjects with ongoing life-threatening bleeding (bleeding resulting in hemodynamic compromise requiring intervention or any intracranial hemorrhage):

- Withhold study drug and all antiplatelets/anticoagulants;
- Institute standard of care for life-threatening bleeding (large bore IV or central venous line, type and crossmatch blood, admit to the intensive care unit, provide hemodynamic and respiratory support);
- Administer antidotes if applicable (eg, administer protamine if the subject had recently received heparin);

- Administer packed red blood cells (or whole blood) as needed.

If life-threatening bleeding persists, it is recommended to contact the ITREAS Medical Support Line (+32 495 54 74 51) to discuss subject management. Use of prothrombin complex concentrates (PCCs), recombinant Factor VIIa, other factor procoagulants, or antifibrinolytics (depending upon the clinical situation and local availability) should be considered in consultation with an expert and the ITREAS Medical Support Line.

5.3.2. Emergency Surgery

If an urgent surgical intervention is needed, anticoagulant therapy should be discontinued and the surgery should be deferred, if possible, until at least 12 hours and ideally 24 hours after the last administration of anticoagulant therapy. There is no reversal agent for edoxaban. Protamine can be used to (partially) reverse the effect of LMWH. Depending upon the clinical situation and local availability, the use of factor procoagulants or other measures can be considered in case of the recent intake of edoxaban prior to the surgical procedure. It is recommended to consult the ITREAS Medical Support Line (+32 495 54 74 51) in case of urgent surgery.

5.3.3. Suspected Recurrent VTE

In case of suspected recurrent VTE, the Investigator may decide to treat the subject according to the standard of care.

5.4. Therapeutic Management of Subjects for Planned Interventions

Given the half-life of both study medications and the interval of dosing (ie, once a day) it is advised to withhold the study medications at least 24 hours prior to the planned intervention. Study drug can be resumed upon complete hemostasis and after the assessment of the bleeding risk, ie, after 6 to 24 hours for most minor procedures and after 2-3 days for most surgical procedures that carry a bleeding risk. Antithrombotic therapy other than the study drug can be initiated, eg, a (prophylactic) dose of LMWH, according to the institutional best practice, until re-initiating dosing of the study drug is considered to be appropriate.

It is recommended to consult the ITREAS Medical Support Line (+32 495 54 74 51) in case of any further questions on the management of subjects who need a planned intervention.

5.5. Therapeutic Management of Subjects in Other Critical Situations

Other critical situations could be admission to hospital for acute medical illness or active periods of chemotherapy. In these circumstances gastrointestinal disorders might preclude intake of oral therapy with edoxaban and bridging to LMWH is allowed according to the guidance in Appendix 17.2. In case of doubt it is recommended to contact the ITREAS Medical Support Line (+32 495 54 74 51).

5.6. Therapeutic Management of Subjects Beyond Month 12 and at Global End-of-Treatment

Subjects requiring additional anti-coagulation therapy who complete their treatment and full 12-month post randomization follow-up or whose treatment is truncated due to the global End of Treatment date will be managed according to local practice.

Guidance for switching from edoxaban to other anticoagulants is provided in Appendix 17.2.

Additional guidance for long-term management of cancer subjects with VTE is provided by Lyman, et al.[1]

6. STUDY PROCEDURES

The Schedule of Study Procedures for this study is provided in Appendix 17.7.

6.1. Study Qualification/Pre-randomization

It is expected that most subjects will have had some or all of the study qualification procedures done as part of routine care outside the auspices of this study (for example, diagnostic work-up and associated care for VTE). If these procedures are done prior to randomization, they may be used to randomize the subject to study and begin completion of the eCRF, once the subject has signed the ICF. The subject does not need to repeat recently completed procedures/tests for study qualification. For such subjects it may be possible to combine the study qualification and randomization visits into a single visit.

Any protocol-specified study qualification procedures/tests not already done as part of routine care will be conducted only after the subject signs the ICF and before randomization. Prior to signing the ICF, potential subjects will have the study risks and benefits explained to them, the associated ICF will be reviewed, and all questions answered for them.

The following study qualification procedures must be completed to ensure that the subject is eligible for the study.

- Sign ICF;
- Review inclusion/exclusion criteria, and ensure that the subject qualifies with regard to the clinical laboratory tests for exclusion criteria:
  - Calculated CrCL < 30 mL/min;
  - Platelet count < 50,000/mL
- Review concomitant medications for assessment of exclusion criteria;
- Ensure that the subject has a diagnosis of VTE confirmed by appropriate imaging methods;

The following imaging methods are typically considered part of routine hospital work-up for the management of VTE and/or cancer, and as such, will normally be obtained prior to informed consent as part of the subject's normal standard-of-care.

- For a suspected symptomatic DVT: compression ultrasonography (CUS), venography, or specific computerized tomography (CT) venography.
- For unsuspected DVT: a thrombus detected in the IVC or iliac veins on a (staging) abdominal or pelvic CT will be considered diagnostic. Because of potential flow artifacts and layering of contrast, a suspected thrombus detected in the common femoral vein or more distal can only be considered if confirmatory CUS or (CT) contrast venography diagnostic criteria are also met.

- For suspected symptomatic PE: Computerized tomographic pulmonary angiography (CTPA; also called spiral CT angiography [spiral CT]), ventilation perfusion scan (V/Q scan; if perfusion scan only is done a confirmatory test for leg DVT is required), or catheter pulmonary angiography.

Note: A perfusion scan (without ventilation scan) does not qualify for the diagnoses of PE, unless concomitant DVT is documented.

- For an unsuspected PE: found during a staging-CT a repeat test is not recommended in order to limit radiation and contrast exposure. This incidental finding will only be considered diagnostic if the clot is in a segmental or greater artery, whereas clots in sub-segmental or more peripheral arteries will not be accepted due to risk of a false positive result.

- Record demographic information;
- Record medical/surgical history, including co-morbidities;
- Record description of cancer (date of diagnosis, type, (ie, histologically or cytologically diagnosed solid tumor), location or hematological malignancy, stage (eg, early, regionally advanced, metastatic), details on therapeutic management);
- Based on data completed in the eCRF it will be assessed whether subject meets the criteria for active cancer which will be defined as:
  - Diagnosed with cancer within the past 6 months; or
  - Recurrent, regionally advanced or metastatic disease;
  - Currently receiving treatment or have received any treatment for cancer during the 6 months prior to randomization; or
  - A hematologic malignancy not in complete remission

Note: Subjects not meeting these criteria will be categorized as history of cancer and then cancer should have been diagnosed within the 2 years preceding randomization.

- Perform physical examination including vital signs (sitting BP and heart rate) and record height and body weight (may be performed by an Investigator or other healthcare provider designated by the Investigator);
- Assess the subject for active bleeding, high risk for bleeding, and any other contraindications for treatment with LMWH or edoxaban.

Samples obtained as part of routine care outside study auspices may be analyzed by local laboratories and the results used to qualify the subject provided the tests were performed within 7 days of randomization.

Full documentation for the above study qualification procedures and related results are required, including local laboratory results used to qualify the subject. Therefore, the eCRF must be completed for every subject with a signed ICF.

An index event dossier must be compiled, which includes copies of the diagnostic tests done to confirm the index VTE. The dossier will be reviewed by the CEC. Instructions for completing the dossier package will be provided in the outcome reporting manual. Due to logistical constraints, adjudication of index events will be performed after randomization; hence, the adjudicated result will not be used to qualify the subject for the study, but rather to subsequently define the outcome analyses sets.

The index event package must also contain copies of test reports or hospital letters confirming the subject's cancer diagnosis. The investigational site should ensure that any personal subject identification other than subject number and initials are removed from the index event dossier.

Based on the inclusion criterion that long term treatment with LMWH is intended to be given, it is expected that a large proportion of subjects will meet the criteria for active cancer. Nevertheless, the percent of subjects with active cancer will be monitored during the study by a medical monitor who will report to the SMCC chair. If necessary, the SMCC will take appropriate actions to ensure that the proportion of subjects with active cancer is sufficient (ie, > 75%) to draw valid conclusions in the active-cancer population

6.2. Day 1/Randomization

Before randomization, the Investigator will ensure that all protocol-specified pre-randomization requirements and procedures are met and/or completed. For subjects who meet all the inclusion criteria and none of the exclusion criteria, the following will be performed on the day of randomization, prior to actual randomization.

- Complete the IXRS Randomization Visit worksheet including review of subject's age, bleeding risk profile, body weight, calculated CrCL, and concomitant medications;
- Record vital signs (sitting BP and heart rate) and weight;
- Assess and record ECOG Performance Status (see Appendix 17.6 for the ECOG performance scale);
- Collect serum sample for archiving by QLabs for later testing if necessary. Use the QLabs pre-dose Day 1 kit and ship the sample to QLabs;
- Record the following local laboratory results in the eCRF:
  - Serum chemistry
    - Total bilirubin (direct and indirect)
    - Alanine transaminase (ALT)
    - Aspartate transaminase (AST)
    - Alkaline phosphatase (ALP)
    - Serum creatinine
    - CrCL

- Hematology and platelet count
  - Hematocrit
  - Hemoglobin
  - White blood cell (WBC) count with differential
  - Platelet count

If all procedures and tests done before randomization confirm the subject's eligibility for the study, access the IXRS, register the subject for study qualification, and obtain the subject identification number.

The following activities and/or assessments will be performed at/during randomization:

- Record AEs and treatments (drug and non-drug) given for AEs;
- Record prior targeted medications taken within 30 days before randomization;
- Record date and time for Day 1 dose of study drug;
- Dispense study drug (dalteparin or edoxaban) and record amount (number of tablets and syringes) dispensed;
- Explain the study medications and the proper daily dosing to the subject and confirm that the subject understands the proper daily dosing of study medication, including when to stop LMWH and begin edoxaban dosing;
- Instruct subject to bring unused study drugs to each study visit;
- Provide subjects with a patient information booklet, which will contain the following information:
  - The study outline in layman’s terms;
  - The local medical contact person and emergency telephone number;
  - The visit schedule provided by the IXRS (fax or email with dates of telephone and/or hospital visits);
  - How to recognize and report signs and symptoms of possible recurrent symptomatic PE/DVT or bleeding;
  - Instructions to keep empty medication packages;
  - How to use the study medication;
  - A short list of prohibited medications.
- Provide subjects with a subject identification safety card.

Investigators will maintain a confidential subject identification code list of names of all the subjects randomized to study to allow the Investigator to reveal the identity of any subject when necessary.

6.3. Treatment Period

The treatment period begins with the first dose of LMWH (dalteparin or other LMWH depending on randomized treatment assignment) after randomization and ends with the last dose of study drug at the time of permanent discontinuation of study drug. During the treatment period, the subject will be instructed to bring all study drug supplies to each scheduled (every 3 months) study assessment. Outcome and other event reporting (eg, VTE, bleeding, AEs) will be done throughout the study as soon as site personnel learn of the event. Recording of AEs and treatments (drug and non-drug) given for AEs will be done throughout the study.

Subjects who permanently discontinue study drug will be followed for efficacy and safety outcomes and SAEs by visit or telephone contact at least once every 3 months until Month 12, except as noted in Section 3.1.2.1. If the subject has an on-site visit, obtain vital signs and any laboratory assessments deemed appropriate by the Investigator. Ideally, all subjects should have their final EOT post-randomization visit completed in person either in-clinic or home visit.

6.3.1. Day 31 (± 3) Visit

At Day 31 following randomization, all subjects should be seen by qualified medical personnel for the following procedures:

- Assess for AEs and outcome events;
- Record targeted concomitant medications, any interruptions in chemotherapy treatment due to a VTE or bleed event or medication given in association with an AE/SAE;
- Assess study drug dosing compliance;
- Record interruptions of edoxaban or dalteparin with the date of last dose and the date of the first dose of resumption of drug (see also Section 4.2.1.1);
- Capture healthcare resource utilization as appropriate;
- Assess ECOG performance status;
- Monitor and record hemoglobin/hematocrit, platelet counts, weight, serum creatinine, creatinine clearance, and P-gp inhibitor use and determine if a study drug dose adjustment is necessary;
- Dispense study medications and down-titrate dalteparin subjects to maintenance dose.

6.3.2. Months 3, 6, and 9 (± 7 days)

All subjects should be seen by qualified medical personnel for the following procedures:

- Assess for AEs and outcome events;

- Record targeted concomitant medications, any interruptions in chemotherapy treatment due to a VTE or bleed event or medication given in association with an AE/SAE;
- Assess study drug dosing compliance (if the subject is still on study treatment);
- Record interruptions of edoxaban or dalteparin with the date of last dose and the date of the first dose of resumption of drug (if the subject is still on study treatment; see also Section 4.2.1.1);
- Capture healthcare resource utilization as appropriate;
- Assess ECOG performance status;
- Monitor and record hemoglobin/hematocrit, platelet counts, weight, serum creatinine, creatinine clearance, and P-gp inhibitor use and determine if a study drug dose adjustment is necessary (if the subject is still on study treatment);
- Liver function test monitoring (only at Month 6 if the subject is still on study treatment):
  - ie, record (or collect a serum sample for) transaminase (ALT/AST), alkaline phosphatase, and bilirubin levels
- Dispense study medications (if the subject is still on study treatment).

6.4. End of Treatment/Month 12 (± 7 days)

All subjects should be seen by qualified medical personnel for the following procedures at Month 12 or whenever study treatment is permanently discontinued. Subjects permanently discontinuing study treatment before Month 12 will still be followed until Month 12 or the global EOT date whichever occurs first.

- Assess for AEs and outcome events;
- Record targeted concomitant medications, any interruptions in chemotherapy treatment due to a VTE or bleed event or medication given in association with an AE/SAE;
- Collect all unused study drug (if the subject is still on study treatment)
- Assess study drug dosing compliance (if the subject is still on study treatment);
- Record interruptions of edoxaban or dalteparin with the date of last dose and the date of the first dose of resumption of drug (if the subject is still on study treatment; see also Section 4.2.1.1);
- Count unused edoxaban tablets and dalteparin syringes and record in the IXRS drug accountability module (if the subject is still on study treatment);
- Capture healthcare resource utilization as appropriate;

- Assess ECOG Performance Status;
- Update cancer status/stage;
- Liver Function Test monitoring if the subject is still on study treatment:
  - ie, record (or collect a serum sample for) transaminase (ALT/AST), alkaline phosphatase and bilirubin.

6.5. Follow-Up

Not applicable.

6.6. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC.

A deviation to any key protocol procedures, or waiver to any stated eligibility criteria will not be allowed except as noted below and where necessary to eliminate immediate hazard(s) to the subject.

Subjects for whom experimental anticancer treatment is instituted after randomization to the cancer VTE trial will remain in the study and followed for 12 months or the global EOT date, whichever occurs first. The decision whether to discontinue the VTE study treatment will be at PI discretion according to local regulations.

Sponsor must be notified of any unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits).

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

If a subject was ineligible or received the incorrect dose of investigational treatment, and had at least 1 administration of investigational product, the patient should be followed until study discontinuation.

The Investigator should notify the IECs/IRBs of deviations from the protocol in accordance with local procedures.

7. OUTCOME ASSESSMENTS

Subjects with suspected recurrent PE/DVT will undergo objective testing to assess the recurrent episode. In subjects with bleeding additional examinations will be done if deemed necessary by the investigator (eg, hematology blood sample, diagnostic imaging/scoping). In subjects with other suspected outcomes such as death, cardiovascular events, or other thrombotic events the diagnostic work-up will be conducted according to the hospital routine.

For all suspected events an adjudication dossier must be prepared for shipment to the CEC. This dossier will contain the following documentation:

- copies of all diagnostic imaging (reports and/or images);
- clinically relevant notes/hospital letters/ laboratory reports/medical records.

Details regarding the definitions of the study outcomes and how they will be assessed are provided in the CEC Charter. The requirements for testing and reporting are provided in the Outcome Reporting Manual and will be provided to all sites.

7.1. Primary Outcome Variable(s)

The primary study outcome is the composite of recurrent VTE and major bleeding.

Recurrent VTE is either:

- symptomatic confirmed (new) DVT or (new) PE;
- unsuspected (new) proximal DVT
  - Unsuspected DVT is a DVT coincidentally detected during other investigations (eg, abdominal or pelvic CT for cancer staging). This DVT will only be included as an outcome if it concerns a (new) clot located in the popliteal or more proximal leg veins. A thrombus detected in the IVC or iliac veins on an abdominal or pelvic CT does not require additional confirmation. A thrombus detected in the common femoral vein or more distal veins can only be confirmed if CUS (or venography) diagnostic criteria are also met.
- unsuspected (new) PE;
  - unsuspected PE is an embolism coincidentally detected during other investigations (eg, CT for cancer staging), that involves segmental or more proximal pulmonary arteries.
- fatal PE (including unexplained death for which PE cannot be ruled out).

Major bleeding is defined as overt bleeding and:

- associated with a decrease in hemoglobin of $\geq$ 2 g/dL, or
- leading to a transfusion of $\geq$ 2 units of packed red blood cells or whole blood, or

- occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- contributing to death.

7.2. Secondary Outcome Variable(s)

Secondary outcome variables include:

- Recurrent VTE;
- Major bleeding;
- CRNM bleeding;
- Major + CRNM bleeding;
- All bleeding;
- Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE -related death;
- Mortality from all causes;
- Recurrent DVT;
- Recurrent PE;
- Healthcare resource utilization for potential recurrent VTE and bleed events.

7.3. Other Outcome Variable(s)

Other outcome variables include:

- Cardiovascular events (myocardial infarction, stroke, SEE [see Appendix 17.5.1]);
- Thrombotic events at other locations (see Appendix 17.5.2);
- Reason for permanent early discontinuation of study drug.

8. PHARMACOKINETIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Variable(s)

Not applicable.

8.2. Pharmacodynamic (PD) Variable(s)

Not applicable.

8.3. Biomarker and Exploratory Variable(s)

Not applicable.

9. SAFETY ASSESSMENTS

9.1. Adverse Events

This study will follow a targeted approach to AE and SAE reporting. All AEs occurring after the subject signs the ICF and through Month 12 or the global EOT date, whichever occurs first (see Sections 4.2.2.1 and Section 6.4), whether observed by the Investigator or reported by the subject, will be recorded on the Master Event/AE page of the CRF if they fulfill 1 of the following criteria: 1) meet seriousness criteria (see Section 9.4.2) or result in interruption or discontinuation of study drug (edoxaban or dalteparin)) [Events that are assessed by the investigator to be related to the underlying cancer or treatment of the underlying cancer do not meet criteria for targeted AE reporting, as defined in Section 9.4.2]; 2) meet criteria as a study outcome (see Section 3.1.4); or 3) an event of special interest (see Section 9.3).

All laboratory and vital sign values should be evaluated by the Investigator regarding clinical significance. Isolated abnormal laboratory results or vital sign findings should be reported as AEs if they are clinically significant, and 1) meet seriousness criteria (see Section 9.4.2); or 2) result in interruption or discontinuation of study drug (edoxaban or dalteparin) unless related to underlying cancer or other pre-existing condition. Clinically significant abnormal laboratory findings associated with the subject's cancer or other pre-existing conditions will not be reported as AEs or SAEs unless judged by the Investigator as more severe than expected for the subject's condition and meet the criteria for targeted AE and SAE reporting. Laboratory results that are defined as an AE of special interest (AESI) ie, combined elevations of aminotransferase and bilirubin should be reported regardless of causality as described in Section 9.3.1. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history. All SAEs are to be reported according to the procedures in Section 9.5 Serious Adverse Event Reporting-Procedure for Investigators.

All SAEs occurring after informed consent for general study participation is obtained are to be reported according to the procedures in Section 9.5. Always report the diagnosis as an AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. A pre-planned (prior to signing the Informed Consent Form) procedure or treatment requiring hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for Definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. When a subject dies from disease progression of pre-existing cancer with no other immediate causes, "disease progression" should be reported as an SAE. In addition, any serious, untoward event that

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

At each visit, the Investigator or appropriately qualified designee will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs 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.

9.2. Safety Outcomes

9.2.1. Bleeding Outcomes

All suspected bleeding events, irrespective of the clinical relevance assessed by the Investigator, must be reported and will be reviewed and classified by the CEC as major, clinically relevant non major, nuisance or no bleeding event.

Details regarding the classification of bleeding events and how these events will be assessed are provided in the CEC Charter. The requirements for reporting bleeding events are provided in the Outcome Reporting Manual and will be provided to all study sites.

9.3. Events of Special Interest

9.3.1. Combined Elevations of Aminotransferase 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 without evidence of cholestasis (ALP > 2 x ULN is considered evidence of possible cholestasis) and without alternative etiology for hepatocellular damage.

Combined elevations of aminotransferases and bilirubin whether or not causally related, should always be reported to the Sponsor as soon as possible but within 24 hours of awareness if they meet the following criteria (see procedures outlined in Section 9.5 for SAE reporting):

- The event meets seriousness criteria;

- The event (serious or non-serious) results in study drug interruption or discontinuation;
- The event is non-serious but there is no evidence of cholestasis (ALP > 2 x ULN) and without alternative etiology for hepatocellular damage.

In cases of liver laboratory abnormalities, or evidence of liver dysfunction, it is important to ensure that the nature and the extent of liver injury is identified and study subjects are monitored until the liver laboratory assessments are stabilized (Please refer to Section 4.2.2.1).

9.4. Definitions

9.4.1. Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

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

9.4.2. Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

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

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the

definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

The following are not considered AEs or SAEs in the context of this study:

- Hospitalization for a pre-planned procedure or diagnostic tests (including for cancer staging, eg, CT scan, Magnetic Resonance Imaging, gastroscopy, cystoscopy, bronchoscopy, etc) or treatment for pre-existing conditions (eg, chemotherapy, radiation therapy) should NOT be reported as SAEs;
- Hospitalization and/or intervention for diagnostic work-up or treatment of worsening underlying cancer or complications of cancer treatment (eg, work-up for febrile neutropenia, transfusion for anemia, MUGA scan to rule out cardiomyopathy) should NOT be reported as SAEs.

9.4.3. Adverse Event Severity

The following definitions should be used to assess intensity of AEs per the NCI CTCAE criteria:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

9.4.4. Causality Assessment

The Investigator should assess causal relationship between an adverse event and the study product LMWH/edoxaban 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 study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).
  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- 2 = Not Related:
  - The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical

state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding the Study Product

- 1 = Dose Not Changed: No change in study drug dosage was made.
- 2 = Drug Withdrawn: The study product was permanently stopped.
- 3 = Dose Reduced: The dosage of study product was reduced.
- 4 = Drug Interrupted: The study product was temporarily stopped.
- 5 = Dose Increased: The dosage of study product was increased.

9.4.6. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The subject fully recovered from the adverse event with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the adverse event are still present and observable.
  - Include sequelae/residual effects.
- 3 = Not Recovered/Not Resolved
  - The adverse event itself is still present and observable.
- 4 = Fatal
- 5 = Unknown

9.4.7. Other Action Taken for Event

- 1 = None.
  - No treatment was required.
- 2 = Medication required.
  - Prescription and/or over-the-counter medication was required to treat the adverse event.
- 3 = Other.

9.5. Serious Adverse Event Reporting–Procedure For Investigators

All AEs, SAEs, AESIs, and study outcomes that meet the criteria specified above will be captured in the eCRF.

Study outcomes are clinically anticipated events and will be periodically reviewed by the DMC to ensure prompt identification of any clinically concerning safety issues. Study outcomes (suspected recurrent DVT or PE, bleeding, MI, stroke, SEE [see Appendix

17.5.1], and thrombotic events at other locations [see Appendix 17.5.2]) will be exempted from expedited safety reports of suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities, Investigators, IECs, and IRBs. All SAEs resulting in death, regardless of whether they are waived endpoint events, will be captured in the Sponsor's global safety database.

The following types of events should be reported by the Investigator in eCRF within 24 hours of awareness to support expedited safety reporting:

- SAEs (see Section 9.4.2 for definition)
- Liver enzyme abnormalities/liver dysfunction events [ALT or AST > 3x ULN with simultaneous TBL > 2 x ULN] meeting the following criteria:
  - The event meets seriousness criteria;
  - The event (serious or non-serious) results in study drug interruption or discontinuation;
  - The event is non-serious but there is no evidence of cholestasis (ALP > 2 x ULN) and without alternative etiology for hepatocellular damage.

Call Quintiles (telephone number will be provided per country, per region; please refer to Study Manual for an appropriate phone number) for any questions on SAE reporting. Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

In the event that eCRF is unavailable, report SAEs by faxing the paper Daiichi Sankyo Serious Adverse Event Report (SAVER) Form to Quintiles using the provided fax cover sheet and the appropriate fax number provided for your country (please refer to Study Manual for an appropriate fax number). Once eCRF becomes available, please enter SAEs reported on the SAVER Form into eCRF as soon as possible.

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

Daiichi Sankyo and/or Quintiles will inform Investigators, IRBs (Institutional Review Board)/ECs, and regulatory authorities of any Suspected Unexpected Serious Adverse Event Reactions (SUSARs) occurring in other study centers or other Daiichi Sankyo studies of the investigational product (excluding waived study outcomes per Section 9.5), as appropriate per local reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the investigational product, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

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

9.6. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving investigational product and through Month 12 or the global EOT date, whichever occurs

first, or, within 30 days of last dose if it occurred less than 30 days of the global EOT date.

Although pregnancy is not technically an adverse event, 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 female subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, 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 SAEs outlined in Section 9.5.

9.7. Clinical Laboratory Evaluations

Local laboratory results and reference ranges for the analytes outlined in Sections 6.2, 6.3.1, 6.3.2, and 6.4 will be recorded in the eCRF.

9.8. Vital Signs

Vital sign data will consist of heart rate, BP, and height. Weight will also be recorded in order to make determinations regarding study drug dose adjustments.

9.9. Electrocardiograms

Routine ECGs are not required but will be recorded in the eCRF when appropriate.

9.10. Physical Findings

A physical examination, conducted prior to or at the time of randomization by the Investigator or other qualified health care provider designated by the Investigator, will consist of assessment of each of the relevant major body systems.

9.11. Other Safety Assessments

Other safety assessments will be conducted as necessary.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. Analysis Sets

11.1.1. Randomized Analysis Set

The randomized analysis set includes all subjects randomized to treatment.

11.1.2. Modified Intention-to-Treat Analysis Set

The mITT Analysis Set includes all randomized subjects who receive at least 1 dose of study drug[1].

11.1.3. Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set includes all randomized subjects who receive at least 1 dose of study drug, who have not experienced treatment misallocation, and for whom the index DVT or PE event at baseline was confirmed by the CEC. Treatment misallocation is defined as a subject taking incorrect treatment during the entire study period.

11.1.4. Safety Analysis Set

The Safety Analysis Set includes all randomized subjects who receive at least 1 dose of randomized study drug. Analyses will be based on the randomized treatment, unless a subject inadvertently receives the incorrect drug during the entire study, in which case, the subject will be grouped according to the treatment actually received.

11.2. General Statistical Considerations

The efficacy analyses will be based on the mITT and PP Analysis sets.

The safety analyses will be based on the Safety Analysis Set.

The data analysis will be performed by a CRO under the guidance of the study biostatistician. Data analyses will be performed using software SAS Version 8.0 or higher.

11.3. Study Population Data

The number of subjects in each analysis set will be presented by treatment group. Subjects excluded from the analysis sets will be listed and summarized by treatment group and reason for exclusion. The number and percentage of randomized subjects who discontinued treatment prematurely will be tabulated by main reason for discontinuation and treatment group. Demographic and baseline characteristics (including risk factors) will be summarized by treatment group using descriptive statistics. No statistical tests will be performed.

[1] Study drugs include the LMWH prescribed by the PI as the edoxaban lead-in, edoxaban, and dalteparin.

11.4. Outcome Analyses

11.4.1. Primary Outcome Analyses

The primary outcome analysis will be based on the mITT Analysis Set. In this analysis, the time to the first event of the composite primary outcome (recurrent VTE [symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, unsuspected PE, fatal-PE] or major bleed) will be analyzed using a Cox's proportional hazard model including treatment group, and the stratification factors as covariates. The time to first event is defined as the time (days) from the day of randomization to the first event experienced by a subject during the 12-month study period. Subjects who do not have a primary outcome during the 12-month study period will be censored at Day 365, or the last day the subject had a complete assessment for study outcomes, or the global EOT date, whichever comes first. Subjects lost to follow-up, subjects who died because of reasons other than DVT/PE, or subjects who withdrew informed consent before the end of the 12-month treatment period and who did not have a primary outcome, will be censored at the last day the subject had a complete assessment for study outcomes. The LMWH/edoxaban-to-comparator Hazard Ratio will be computed with 95% CI (two-sided testing), based on this model. LMWH/edoxaban will be considered non-inferior to comparator if the upper limit of the CI is < 1.5.

The assumption of proportional hazards will be checked using graphical methods as log (log)-plots and plots of scaled Schoenfeld residuals for the primary analysis. If the assumption is seriously violated, then a logistic model including treatment group and the stratification factors as covariates will be used. The impact of selected baseline covariates on the primary outcome will be described by calculating adjusted Hazard Ratios and corresponding 95% CI of the treatment effect.

The frequencies of the each components contributing to the primary outcome will be described.

The following sensitivity analyses will be performed for the Primary Outcome:

- On-Treatment events based on the PP Analysis Set will be analyzed using the counting process approach of the Cox proportional hazards regression model including treatment group, and the stratification factors as covariates. An On-Treatment event is defined as the event occurring during the time period the subject is taking study drug up to 3 days after their last dose for that time period. Only events occurring prior to or on Day 365 will be included into this analysis. Subjects who do not experience an On-Treatment event will be censored at Day 365, or the time study drug is permanently discontinued plus 3 days or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global end of treatment, whichever comes first.
- Events occurring during the first 6 months (180 days) based on the mITT Analysis Set will be analyzed using the same statistical model as the primary analysis of the primary outcome. The time to event is defined as the time (days) from the randomization to the first event during the first 6 months after

randomization. Subjects who do not experience an event until Day 180 will be censored at Day 180, or the time study drug is permanently discontinued or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, whichever comes first.

11.4.2. Superiority Analysis of the Primary Outcome

If non-inferiority in the primary outcome is established, LMWH/edoxaban will be compared to dalteparin for superiority (α=0.05, two-sided) with regard to the time to an event in the composite clinical outcome of recurrent VTE (symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, unsuspected PE, and fatal-PE) or major bleed during the 12-month study period. This analysis will be based on the mITT Analysis Set using the same proportional hazard model as for the primary outcome.

11.4.3. Secondary Efficacy Outcome Analyses

Summary statistics will be provided for following efficacy outcomes:

- recurrent VTE;
- event-free survival, the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE -related death;
- recurrent DVT;
- recurrent PE.

The impact of cancer status on the primary outcome will also be assessed.

A description of all planned analyses will be incorporated into the SAP.

11.5. Pharmacokinetic Analyses

Not applicable.

11.6. Safety Analyses

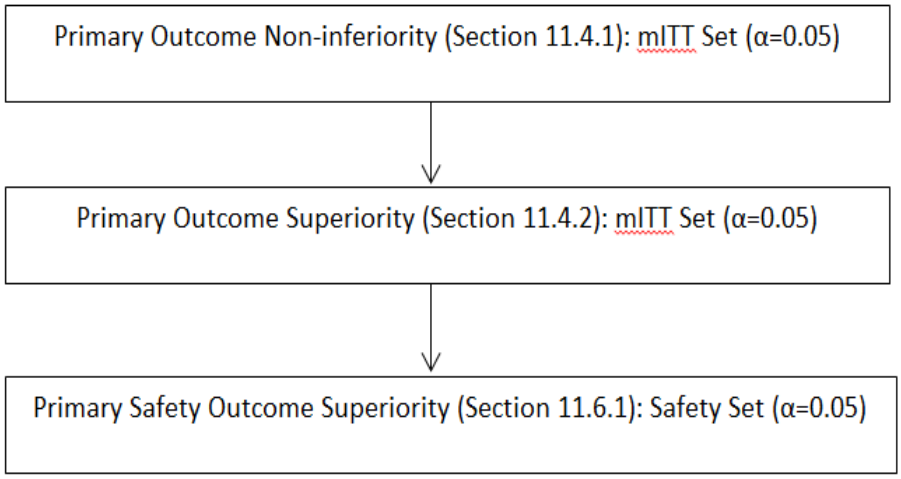
All safety analyses will be performed on the Safety Analysis Set.

11.6.1. Analysis of the Primary Safety Outcome

The primary analysis of the primary safety outcome is based on an "On-Treatment" approach. The "on-treatment" major bleeding events will be compared between treatment groups for superiority (α=0.05, two-sided) for subjects in the Safety Population, using the counting process approach of the Cox proportional hazards regression model including treatment group, and the stratification factors as covariates. However, subjects will be censored 3 days after the day of permanent study medication discontinuation.

To control study-wise type I error, the testing for non-inferiority and superiority will follow the plan as described in Figure 11.1. All tests will be two-sided.

Figure 11.1: Non-Inferiority and Superiority Testing of LMWH/Edoxaban versus Dalteparin



11.6.2. Analysis of Secondary Safety Outcomes

Incidence and Hazard Ratio (with 95% CI) for the following outcomes will be calculated based on the Safety Analysis Set and On-Treatment-approach using the same counting process approach of the Cox proportional hazards regression model as for the primary safety outcome analysis:

- Major bleeding;
- Clinically relevant non-major bleeding;
- Major + clinically relevant non-major bleeding;
- All bleeding;
- Mortality from all causes.

Healthcare resource utilization for potential recurrent VTE and bleeding events will be analyzed separately.

11.6.3. Exploratory Analyses for Safety Outcomes

The incidence of cardiovascular events (myocardial infarction, stroke, SEE) and thrombotic events at other locations will be summarized by treatment.

The reason for permanent early discontinuation of study drug will be summarized by treatment group.

Details are specified in the SAP.

11.6.4. Adverse Event Analyses

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Any AE that occurs during the study is a study AE. Treatment-emergent adverse events (TEAEs) are defined as an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state. The incidence of TEAEs will be presented for the Safety Analysis Set by treatment group, by relationship to the study drug, and by severity. Frequent TEAEs (reported by at least 5% of subjects in any treatment group) will be summarized by treatment group. Adverse events that start or worsen after the third day following the calendar date of any "last dose" and before the date of the next "first dose" are defined as post-treatment AEs. Because a subject can have study drug interruptions, it will be possible to have a post-treatment AE that occurs at an earlier calendar date than a TEAE.

The incidence of death, SAEs, drug-related SAEs, and AEs leading to discontinuation of study drug will be summarized by treatment group. All AEs will be included in a data listing and a listing to display the coding of AEs will be prepared as well.

11.6.5. Clinical Laboratory Evaluation Analyses

The clinical laboratory evaluations at each scheduled visit and the change from baseline will be summarized for the Safety Analysis Set by treatment group. Shift tables (low, normal, and high) will be provided for each treatment group for selected clinical laboratory parameters. The number and percentage of subjects with clinically relevant abnormal clinical laboratory values while on study drug will be calculated for each treatment group for selected clinical laboratory parameters. All abnormal clinical laboratory values will be presented in a listing.

11.6.6. Vital Sign Analyses

Vital signs at each evaluation point and the change from baseline will be summarized for the Safety Analysis Set by treatment group. The number and percentages of subjects with abnormal vital signs while on study drug will be summarized by treatment group.

11.6.7. Physical Finding Analyses

Abnormalities in physical examinations by body system will be listed.

11.7. Other Analyses

11.8. Interim Analyses

No formal interim analysis is planned. Risk-benefit will be evaluated by the DMC, which will give recommendations on a regular basis to the Executive Committee. Access to interim tabular risk-benefit data will be restricted. The procedures of the DMC will be described in its charter.

11.9. Data and Safety Monitoring Board

An independent DMC will be created to further protect the rights, safety, and well-being of subjects who will be participating in this study. The DMC will be composed of qualified scientists, who are not Investigators in the study and not otherwise directly associated with the Sponsor. The DMC will be described in detail in the DMC Charter.

Activities of the DMC will be documented. This documentation will include data summaries and analyses provided to the committee as well as minutes of the meeting.

The DMC can recommend study or treatment regimen/group termination to the Executive Committee based on pre-specified concerns described in the DMC Charter.

11.10. Subgroup Analyses for Efficacy and Safety

Exploratory subgroup analyses, relative to primary study outcomes and key safety outcomes may include, but are not limited to, treatment group comparisons within subject characteristics (age, gender, geographic region, dose adjustment) as described in the SAP.

11.11. Sample Size Determination

Assuming a hazard ratio of 1, a total of 191 overall primary events are projected to accrue in the mITT analysis set which will ensure at least 80% power for the primary analysis at a non- inferiority margin for the hazard ratio of 1.5 and a Type I error of 0.05 (two-sided).

Assuming a primary combined outcome rate (recurrent VTE or major bleed) of 20.0%, a total of 1000 subjects are expected to be randomized to study treatment in order to accrue 191 overall primary events in the mITT analysis set.

12. DATA INTEGRITY AND QUALITY ASSURANCE

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

This study will utilize Quintiles Data-driven Trial Execution (DTE), which is Quintiles model for risk-based monitoring.

Quintiles' DTE and Daiichi Sankyo will begin with a risk assessment to evaluate the scientific and operational risks of the study. During this risk assessment key data points for the study will be identified and the optimum method for monitoring (eg, remote, on-site, and/or centralized monitoring processes) each key data point will be determined. Key data points are data items that are critical to study analysis, indicate if the objectives of the study have been met, support patient safety, and/or are deemed as a priority for monitoring.

12.1. Monitoring and Inspections

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

The monitor is responsible for conducting both onsite and remote monitoring visits 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 frequency of monitoring visits will be dependent on the activities at the site. At a minimum the monitor will visit active sites on an annual basis. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

Transcription-Based source data verification (SDV) is a strategic monitoring task that will be used to detect transcription errors between the source documents and the eCRF. SDV will be performed on 100% of data for a sample of enrolled subjects at each site. The sample size may be increased where issues are identified.

Source data review (SDR) is an on-site monitoring process in which source documentation is reviewed to ensure that the site's process for documenting source notes is appropriate and that the site is adhering to the requirements of the protocol. The SDR will be performed on the same subjects as SDV. The SDR may be performed on additional subjects where issues are identified.

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

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

Monitoring triggers consisting of essential operational data elements will be used to assess site performance, data quality, and patient safety. Monitoring triggers may independently trigger a site contact or monitoring visit.

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 (eg, pharmacy, drug storage areas, laboratories, etc) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.2. Data Collection

The eCRF completion and query resolution should be kept current to enable the monitor to review the subject's status throughout the course of the study and to enable review of the data by Clinical Data Management.

12.3. Data Management

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

To ensure the quality of clinical data across all subjects and sites, two levels of review will be performed:

The first level review will comprise of traditional data management review. The second level review is a manual check for clinical congruency of the data.

Both the first and second levels of the Clinical Data Management review will be performed on subject data according to specifications agreed by Sponsor and CRO. Data will be vetted both electronically and manually; eCRFs data will be electronically vetted by programmed data rules within the Electronic Data Capture (EDC). Queries generated by rules and raised by reviewers will be generated and resolved within the EDC application. During these reviews, subject data will be checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the Clinical/Data Management review process, eCRFs queries will be raised and resolved within the EDC application.

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

Serious AEs in the clinical database will be reconciled with the safety database.

All Adverse Events and medical history entries will be coded using MedDRA. Concomitant medications, when necessary, will be coded using the World Health Organization Drug Reference (WHODRUG) List.

12.4. Study Documentation and Storage

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

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

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

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

12.5. Record Keeping

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

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with Quintiles. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

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

14. PUBLICATION POLICY

A site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until 1 year after the study has ended, whichever occurs first. Therefore, the site will have the opportunity to publish the results of the study, provided that Daiichi Sankyo has had the opportunity to review and comment on the site's proposed publication prior to its being submitted for publication with the prior advice of Daiichi Sankyo Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

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 protocol. A protocol amendment may be implemented after it has been approved by the IRB/EC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/EC within 5 working days. The Sponsor will ensure the timely submission of amendments to regulatory authorities.

15.2. Address List

15.2.1. Sponsor

Daiichi Sankyo Pharma Development
399 Thornall Street
Edison, NJ 08837
Phone: 732-590-5000

15.2.2. CRO

Quintiles, Inc.
4820 Emperor Blvd
Durham, NC 27703
Phone: 919-998-2000

15.2.3. Academic Research Organization (ARO)

ITREAS
Wg-Plein 188
Amsterdam 1054 SC
The Netherlands
Phone: +31 20 233 0563

16. REFERENCES

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17. APPENDICES

17.1. Additional Information on Investigational Products

17.1.1. Fragmin Package Insert

The Fragmin (dalteparin) package insert can be accessed at the following link: http://www.medicines.org.uk/emc, then typing Fragmin in the search field.

17.2. Transition from Edoxaban to Other anticoagulants

17.2.1. Edoxaban to VKA

Discontinue edoxaban and administer a parenteral anticoagulant and VKA at the time of the next scheduled edoxaban dose. Once a stable INR $\geq$ 2.0 is achieved, the parenteral anticoagulant must be discontinued and the VKA continued.

17.2.2. Edoxaban to non-VKA Oral Anticoagulants

Discontinue edoxaban and start the non-VKA anticoagulant at the time of the next scheduled dose of edoxaban.

17.2.3. Edoxaban to Parenteral Anticoagulants

Discontinue edoxaban and start the parenteral anticoagulant at the time of the next scheduled dose of edoxaban.

17.3. Prohibited Concomitant Medications

Specifically excluded concomitant medications and cautions regarding other concomitant medications are provided below. The list in this appendix reflects exclusionary concomitant medications at the beginning of the study. If there are changes to this list during the study, the changes will be provided as an update to this appendix, but will not be considered a protocol amendment.

17.3.1. Antiplatelet Drugs

Dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or IV antiplatelet drug) is prohibited while on study drug. If a clinical indication for dual antiplatelet therapy arises after randomization (eg, placement of an intracoronary stent), study drug should be interrupted and use of open-label LMWH/VKA is permitted at the physician's discretion.

Use of any antiplatelet medication, including aspirin, as single agent antiplatelet therapy is allowed while on study drug.

It is strongly encouraged to restrict the dose of aspirin (if indicated) to $\leq$ 100 mg daily, although higher doses are permitted for a strong clinical indication (eg, development of an acute MI).

Examples of non-aspirin oral antiplatelet agents include the following:

- Thienopyridines: clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel (Effient™)

- Dipyridamole: Persantine®, Aggrenox®
- Pentoxifylline (Trental®)
- Sulfinpyrazone (Anturane®)
- Ticagrelor (Brilinta®)
- Cilostazol (Pletal®)

IV antiplatelet agents include the following:

- Glycoprotein IIb/IIIa inhibitors: Abciximab (ReoPro™), Eptifibatide (Integrilin®), Tirofiban (Aggrastat®)
- PGY12 Inhibitor: Cangrelor
- Dextran

17.3.2. Oral Anticoagulants Other Than Study Drug

Oral anticoagulants including vitamin K antagonists (eg, warfarin), Factor IIa inhibitors (eg, dabigatran), and FXa inhibitors (eg, rivaroxaban, apixaban) after randomization are prohibited (unless used to bridge a temporary study drug interruption). The only allowed oral antithrombotics are the study drugs.

17.3.3. Parenteral Anticoagulants

Parenteral anticoagulants such as heparin, LMWHs, direct thrombin inhibitors, and FXa inhibitors are prohibited except as specifically outlined in the protocol. For instance, LMWHs are allowed as lead-in therapy prior to edoxaban administration. Examples of prohibited parenteral anticoagulant medications, when used contrary to protocol specifications, include the following:

- Low molecular weight heparins: dalteparin (Fragmin®), tinzaparin (Innohep®, Logiparin®), reviparin (Clivarin®), nadroparin (Fraxiparine®), ardeparin (Normiflo®), certoparin (Sandoparin®), parnaparin (Fluxum®)
- Direct thrombin inhibitors: bivalirudin (Angiomax®), argatroban (Acova®), desirudin (Ipravask®), lepirudin (Refludan®)
- FXa inhibitors: fondaparinux (Arixtra®)

17.3.4. Intravenous Fibrinolytics

Examples of fibrinolytics include the following:

- Tissue plasminogen activator (alteplase, Activase®)
- TNK (tenecteplase, TNKase®)
- rPA (reteplase, Retavase®)
- Streptokinase (Streptase®)
- Anistreplase (Eminase®)

If a subject requires treatment with a fibrinolytic agent, then study drug must be interrupted while the subject is taking the fibrinolytic drug and at least 24 hours after administration of a fibrinolytic agent.

17.3.5. NSAIDs (Excluding Aspirin)

While on study drug, NSAIDs cannot be taken for ≥ 4 days per week. Less frequent use of NSAIDs is permitted while on study drug. However, the Investigator should weigh the benefit/risk of NSAID use in combination with an oral anticoagulant for the individual subject. Examples of NSAIDs include the following:

Aceclofenac	Acemetacin	Alclofinac
Amtolmetin	Axapropazone	Benoxaprofen
Bromfenac	Bufexamac	Carprofen
Clonixin	Dexibuprofen	Dexketoprofen
Diclofenac	Diclofenac/Hyaluronic Acid	Diflunisal
Dipyrone	Droxicam	Etodolac
Etofenamate	Felbinac	Felbufen
Fenoprofen	Fentiazac	Floctafenine
Flufenamic Acid	Flurbiprofen or fluribuprofen	Hydrocodone/Ibuprofen
Ibuprofen	Indomethacin	Indoprofen
Isoxicam	Ketoprofen	Ketorolac
Lansoprazole/Naproxen	Lornoxicam	Loxoprofen
Meclofenamate	Mefanamic Acid	Meloxicam
Morniflumate	Nabumetone	Naproxen
Niflumic Acid	Nimesulide	Oxaprozin
Oxycodone/Ibuprofen	Phenylbutazone	Piketoprofen
Pirazolac	Piroxicam	Piroprofen
Prophenazone	Proquazone	Sulindac
Suprofen	Tenidap	Tenoxicam
Tiaprofenac Acid	Tolmetin	Zomepirac

17.3.6. COX-2 Inhibitors

While on study drug, COX-2 inhibitors cannot be taken for ≥ 4 days per week. Less frequent use of COX-2 inhibitors is permitted while on study drug. However, the Investigator should weigh the benefit/risk of COX-2 inhibitor use in combination with an oral anticoagulant for the individual subject. Examples of COX-2 inhibitors include the following:

Celecoxib	Parecoxib
Artilog	Dynastat
Celecox	Rofecoxib
Celebra	Arofex
Celebrex	Ceoxx
Solexa	Coxxil
Etoricoxib	Dolcoxx
Arcoxia	Miraxx
Lumiracoxib	Vioxx
Lumirelax	Vioxxalt
Lumrelax (FM)	Valdecoxib
Lumirem	Bextra

17.3.7. P-gp Inhibitors

Concomitant use of protease inhibitors (such as ritonavir, nelfinavir, indinavir, and saquinavir) anticipated to continue during the course of the study is prohibited. Concomitant use of certain macrolide antibiotics (erythromycin, azithromycin, and clarithromycin) and azole antifungals (ketoconazole and itraconazole) are also prohibited at the time of randomization, but subsequent use of these agents is permitted after randomization with appropriate dose reduction of edoxaban to 30 mg QD. Once treatment with these P-gp inhibitors is complete, the full 60 mg edoxaban dose should be resumed.

The following common P-gp inhibitors that might be administered to study subjects require a reduction in the edoxaban dose to 30 mg QD:

- Tyrosine kinase inhibitors: imatinib, nilotinib, lapatinib, sunitinib, criozitinib, vandetanib
- Hormonal agents: tamoxifen, enzalutamide, abiraterone,
- Immuno-modulating agents: cyclosporine, tracolimus

Once treatment with these P-gp inhibitors is complete, the full 60 mg edoxaban dose should be resumed.

Note: Other agents in these classes may be administered concurrently without reducing the edoxaban dose.

17.4. Precautions and Dose Modifications for Dalteparin

Month 1 – Dalteparin Doses by Weight

Body Weight (kg)	Scheduled Dalteparin Dose (IU)
≤ 46	7500
47 to 56	10000
57 to 68	12500
69 to 82	15000
≥ 83	18000

Months 2-12 – Dalteparin Doses by Weight

Body Weight (kg)	Scheduled Dalteparin Dose (IU)
≤ 56	7500
57 to 68	10000
69 to 82	12500
83 to 98	15000
≥ 99	18000

Precautions and Dose Modifications

Month 1:

In the case of chemotherapy-induced thrombocytopenia, the dalteparin dose should be adapted as follows:

- In subjects receiving dalteparin who experience platelet counts between 50,000 and 100,000/mm^3, the daily dose of dalteparin should be reduced by 2,500 IU until the platelet count recovers to ≥100,000/mm^3.
- In subjects receiving dalteparin who experience platelet counts < 50,000/mm^3, dalteparin should be discontinued until the platelet count recovers above 50,000/mm^3.

Months 2-12:

In the case of chemotherapy-induced thrombocytopenia, the dalteparin dose should be adapted as follows:

- With platelet counts < 50,000/mm^3, dalteparin dosing should be interrupted until the platelet count recovers above 50,000/mm^3.
- For platelet counts between 50,000 and 100,000/mm^3, dalteparin should be reduced as illustrated in the table below in accordance with the subject's weight. Once the platelet count has recovered to > 100,000/mm^3, dalteparin should be re-instituted at full dose.

Table 17.1: Dalteparin Dose Reduction for Platelet Counts Between 50,000 and 100,000/mm^3

Body Weight (kg)	Scheduled Dalteparin Dose (IU)	Reduced Dalteparin Dose (IU)
≤56	7500	5000
57 to 68	10000	7500
69 to 82	12500	10000
83 to 98	15000	12500
≥99	18000	15000

17.5. Definitions of Cardiovascular and Thrombotic Events

17.5.1. Systemic Embolic Event (SEE)

A systemic embolic event is defined as an abrupt episode of arterial insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (eg, atherosclerosis, instrumentation). Arterial embolic events involving the CNS (including the eye), coronary, and pulmonary arterial circulation are not considered SEEs, but will be classified respectively as stroke/TIA, myocardial infarction, and pulmonary embolism. In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusions.

17.5.2. Thrombotic Events at Other Locations

These include:

- Catheter-associated thrombosis
- Cerebral venous and sinus thrombosis
- Retinal vein occlusion
- Upper extremity venous thrombosis

  - axillary, subclavain and brachial vein thrombosis
  - Jugular vein thrombosis
  - Superior caval vein thrombosis
- Abdominal vein thrombosis
  - Splanchnic vein thrombosis
    - Portal vein thrombosis
    - Mesenteric vein thrombosis
    - Splenic vein thrombosis
  - Hepatic vein thrombosis
- Genito-urinary venous thrombosis
  - Renal vein thrombosis
  - Ovarian vein thrombosis
  - Penile vein thrombosis
- Superficial vein thrombosis of the lower or upper limb

17.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

17.7. Schedule of Events

Table 17.2: Schedule of Events

	Treatment Period							
	Pre-randomization	**Day 1 Randomization**	**Day 31 ± 3 days**	**Month 3 ± 7 days**	**Month 6 ± 7 days**	**Month 9 ± 7 days**	**Month 12 ± 7 days**	**EOT[g] ± 7 days**
Informed Consent	X							
Diagnosis of VTE	X							
Inclusion/Exclusion Criteria	X[a]							
Demographic Information	X							
Medical/Surgical History	X							
Physical Examination[b]	X							
Vital Signs/Weight	X	X						
Cancer Status/Stage	X						X	X
Clinical Assessments and ECOG Performance Status		X	X	X	X	X	X	X
IXRS Randomization		X						
LFT Monitoring[c]		X			X		X[h]	
Serum Creatinine/CrCL		X	X	X	X	X		
Hematology and Platelet Count		X	X	X	X	X		
Archive Serum Sample[d]		X[c]						
Prior and Concomitant Medication	X	X	X	X	X	X	X	X
AE Reporting[e]		X	X	X	X	X	X	X
Outcome Events Reporting[e]		X	X	X	X	X	X	X
Healthcare Resource Utilization			X	X	X	X	X	X
Study Drug Dispensing[f]		X	X	X	X	X		

	Treatment Period							
	Pre-randomization	**Day 1 Randomization**	**Day 31 ± 3 days**	**Month 3 ± 7 days**	**Month 6 ± 7 days**	**Month 9 ± 7 days**	**Month 12 ± 7 days**	**EOT[g] ± 7 days**
Study Drug Compliance			X	X	X	X	X	X
Contact IXRS for study drug assignment or to enter subject status changes[g]		X	X	X	X	X		

LFT-liver function test; VTE-venous thromboembolism; AE-adverse event(s); IXRS-Interactive web/voice response system; CrCL-creatinine clearance; ALT-alanine transferase; AST-aspartate transferase; EOT-end-of-treatment; ECOG-Eastern Cooperative Oncology Group.

[a] Review inclusion/exclusion criteria and ensure that the subject qualifies with regard to the laboratory tests for exclusion criteria (CrCl , 30 mL/min; Platelet count < 50,000/mm^3.

[b] Physical examination at pre-randomization may be performed by an Investigator or other healthcare provider designated by the Investigator. The physical examination includes vital signs (sitting blood pressure and heart rate), record height, and record body weight.

[c] ALT/AST, total bilirubin, and alkaline phosphatase at randomization and subsequent assessments.

[d] One serum sample will be collected at randomization for archiving.

[e] AE reporting and Outcome Events Reporting should occur throughout the study and not be restricted to specific visits; capture healthcare resource utilization data for potential recurrent VTE and bleed events.

[f] Study drug assigned by the IXRS will be dispensed as a 3-month supply.

[g] All subjects should be seen by qualified medical personnel for the following procedures at Month 12 or whenever study treatment is permanently discontinued. Subjects who discontinue study treatment before Month 12 will still be followed until Month 12, or until the global EOT date, whichever comes first.

[h] If the subject is still on study treatment.

SUMMARY OF CHANGE
CLINICAL STUDY PROTOCOL

Investigational Product: DU-176b	**Protocol Number:** DU176b-D-U311	
Protocol Title: A Phase 3b, prospective, randomized, open-label, blind evaluator (PROBE) study evaluating the efficacy and safety of (LMW) heparin /edoxaban versus dalteparin in venous thromboembolism associated with cancer		
Sponsor: Daiichi Sankyo Pharma Development 399 Thornall Street Edison, NJ 08837 Phone: 732-590-5000		
Protocol Version Incorporating Current Summary of Changes:	**Number:** 3.0	**Date:** 20 Jan 2016
Preceding Protocol Version:	**Number:** 2.0	**Date:** 17 Dec 2015

CONVENTIONS USED IN THIS SUMMARY OF CHANGES DOCUMENT
The text immediately preceding and following a change to the protocol is included for each change in order to provide the reviewer with a reference point to identify the change in the protocol.
All locations (ie, section/page numbers and/or paragraph numbers) refer to the current protocol version, which incorporates the items specified in this Summary of Changes document.
The original text is from the preceding protocol version.
In the "New Text", all text added to the protocol is bolded.
In the "New Text", text deleted from the protocol is indicated in strikethrough font.

SUMMARY OF CHANGES

This summary of changes document covers changes in the DU176b-D-U311 clinical study protocol (Version 2.0).

NOTE: Rationale of each change corresponds to the appropriate number.

DESCRIPTION/RATIONALE OF EACH CHANGE	
1	Protocol Title (Page 1) and Protocol Synopsis (Study Title, Page 3) The updated protocol title in Version 2.0 was reverted back to original as in Version 1.0 (A Phase 3b, prospective, randomized, open-label, blind evaluator (PROBE) study evaluating the efficacy and safety of (LMW) heparin /edoxaban versus dalteparin in venous thromboembolism associated with cancer) This was done to keep the amended protocol title consistent with previously filed regulatory documents, thereby obviating the need to revise previously submitted regulatory documents as well.
2	Protocol Synopsis, Section 2.1.2, Section 3.1.4.2, Section 7.2, Section 11.6.2 All bleeding was added as secondary objective. This was erroneously missed out in protocol Version 2.0.

STATISTICAL ANALYSIS PLAN

A PHASE 3B, PROSPECTIVE, RANDOMIZED, OPEN-LABEL, BLIND EVALUATOR (PROBE) STUDY EVALUATING THE EFFICACY AND SAFETY OF LOW MOLECULAR WEIGHT HEPARIN (LMWH)/EDOXABAN VERSUS DALTEPARIN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

Protocol Number: DU176b-D-U311

- **Version 1.0, 29 February 2016**

DAIICHI SANKYO PHARMA DEVELOPMENT

Authorization Signature Page

A PHASE 3B, PROSPECTIVE, RANDOMIZED, OPEN-LABEL, BLIND EVALUATOR (PROBE) STUDY EVALUATING THE EFFICACY AND SAFETY OF LOW MOLECULAR WEIGHT HEPARIN (LMWH)/EDOXABAN VERSUS DALTEPARIN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

Authors:

George Zhang, Ph.D. Date
Director, Biostatistics
Daiichi Sankyo Pharma Development

Christine Lui, M.S. Date
Senior Biostatistician
Quintiles, Inc.

Approved by:

Joshua Betcher, Ph.D. Date
Director, Biostatistics
Quintiles, Inc.

Minggao Shi, Ph.D. Date
Executive Director, Biostatistics
Daiichi Sankyo Pharma Development

- **Regulatory History**

Date	Communication

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1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

1.1. Abbreviations

AEs	Adverse Events	Kg	Kilogram
ALP	Alkaline Phosphatase	Mg	Milligram
ALT	Alanine Aminotransferase	min	Minute
AST	Aspartate Aminotransferase	mITT	Modified Intent-to-Treat
ARO	Academic Research Organization	PE	Pulmonary Embolism
CEC	Clinical Events Committee	PK	Pharmacokinetic
CI	Confidence Interval	PROBE	Prospective, randomized, open-label, blind-evaluator (study design)
CrCL	Creatinine Clearance	PT	Preferred Term
CRO	Contract Research Organization	qd	Once daily
CV	Cardiovascular	SAE	Serious Adverse Event
DMC	Data Monitoring Committee	SEE	Systemic Embolic Event
DSPD	Daiichi Sankyo Pharma Development	SI	Standard International
DVT	Deep Vein Thrombosis	SOC	System Organ Class
eCRF	Electronic Case Report Form	TEAE	Treatment-emergent Adverse Event
eDC	Electronic Data Capture	TESAE	Treatment-emergent Serious Adverse Event
IXRS	Interactive Voice/Web Response System	ULN	Upper Limit of Normal
LMW	Low Molecular Weight	VTE	Venous Thromboembolic Event
MI	Myocardial Infarction	WHO	World Health Organization
MedDRA	Medical Dictionary for Regulatory Activities		

1.2. Definition of Terms

Study Drugs: initial Low Molecular Weight Heparin (LMWH) (dosed after randomization), edoxaban, and dalteparin.

Treatment Groups: References within this Statistical Analysis Plan (SAP) to the "LMWH/edoxaban Group" represent those subjects receiving initial Low Molecular Weight Heparin followed by edoxaban. References to the "dalteparin" represent those subjects receiving dalteparin.

Overall Study Period: The time from the randomization date to the last study follow up visit.

Initial 6-Month Study Period: The time from the randomization date to Day 180, or the last study follow up visit, whichever comes first.

On-Treatment Period: The time period the subject is taking study drug up to 3 days after their last dose for that time period. A subject may have multiple periods of drug use if they temporarily interrupt and resume study drug during the study.

2. INTRODUCTION

This Statistical Analysis Plan (SAP) document provides a more technical and detailed description of the statistical analyses as outlined and/or specified in the study protocol Version 3.0 (dated 20 January, 2016).

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is to demonstrate the non-inferiority of edoxaban (preceded by a short course of LMWH) compared with dalteparin for the prevention of the combined outcome of recurrent venous thromboembolism (VTE) or major bleeding in subjects with VTE associated with cancer during a 12-month study period. The LMWH/edoxaban will be considered non-inferior to dalteparin if the upper limit of the two-sided 95% confidence interval (CI) for the hazard ratio is less than 1.5. If non-inferiority is established, LMWH/edoxaban will be compared with dalteparin for superiority.

3.2. Secondary Objectives

The secondary objectives are to compare LMWH/edoxaban to dalteparin with regard to rates of the following endpoints during the 12-month study period:

- Recurrent VTE
- Major Bleeding
- Clinically relevant non-major (CRNM) bleeding;
- Major + CRNM bleeding;
- All Bleeding;
- Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE-related death;
- Mortality from all causes;
- Recurrent deep vein thrombosis (DVT);
- Recurrent pulmonary embolism (PE);
- Healthcare resource utilization for potential recurrent VTE and bleed events.

3.3. Exploratory Objectives

Exploratory objectives include comparing LMWH/edoxaban to dalteparin with regards to:

- Cardiovascular (CV) events (myocardial infarction (MI), stroke, systemic embolic event (SEE));
- Thrombotic events at other locations;
- Reason for permanent early discontinuation of study drug.

4. STUDY DESIGN AND OVERALL STUDY PLAN

4.1. Study Design

This is a multinational, prospective, randomized, open-label, blind-evaluator (PROBE), non-inferiority study comparing edoxaban with dalteparin for prevention of the combined outcome of recurrent VTE or major bleeding in patients with VTE associated with cancer. Adult subjects with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin; cancer should be active or diagnosed within the previous 2 years), and who present with confirmed acute symptomatic or unsuspected lower extremity proximal DVT, confirmed symptomatic PE, or unsuspected PE in a segmental or larger pulmonary artery for whom long-term treatment (at least 6 months) with LMWH is indicated are eligible to participate in this study.

After a subject's eligibility is confirmed, the subject will be stratified by 1) bleeding risk, and 2) the need for dose adjustment:

1. Bleeding risk (assessed at time of randomization)
    - surgery within 2 weeks prior to randomization
    - use of antiplatelet agents (eg, aspirin ≤ 100 mg/day) that will continue during the study
    - brain tumor or brain metastases present at the time of randomization
    - metastatic disease present at the time of randomization
    - regionally advanced cancer present at the time of randomization
    - gastrointestinal cancer at randomization or diagnosed within a 6-month period prior to randomization
    - urothelial cancer at randomization or diagnosed within a 6-month period prior to randomization
    - Avastin (bevacizumab) use at randomization or given within the 6-week period prior to randomization
2. The need for dose adjustment:
    - body weight ≤ 60 kg, or
    - creatinine clearance (CrCL) between 30 and 50 mL/min inclusive
    - concomitant use of P-gp inhibitors

After stratification, subjects will be randomly assigned via interactive voice/web response system (IXRS) in a 1:1 ratio to one of the two treatment groups: LMWH/edoxaban and delteparin.

After randomization, subjects will be assessed at Month 1, Month 3, and then quarterly thereafter for up to 12 months until they complete the study.

The intention is to treat patients for 12 months with the allocated study treatment. Once 1000 subjects are randomized in the study, a global end-of-treatment (EOT) date will be established that ensures a minimum of 6 months of study treatment and follow-up for the final subject(s) randomized. All subjects will complete or permanently discontinue study treatment on or before the EOT date. Subjects requiring additional anti-coagulation therapy who complete their treatment and full 12-month post randomization follow-up or whose treatment is truncated due to the global EOT date will be managed according to local practice.

Approximately 140 study sites in North America, Europe, and Australia/New Zealand are planned to enroll subjects in this study.

4.2. Overall Study Plan

Regardless of the total duration of study drug treatment actually received, efficacy and safety data will be collected on all subjects, including those who temporarily interrupt or permanently discontinue study drug, during the entire 12-month study period following randomization. For all subjects, contacts (visits or phone calls) are scheduled at regular time points (Protocol Appendix 17.7, Schedule of Events). During these contacts, the treatment and clinical course of the subject will be evaluated. Subjects with suspected efficacy or safety endpoints will undergo confirmatory testing. All subjects, including those who temporarily interrupt or permanently discontinue study drug, will be followed up until Month 12, or until the global EOT date, whichever comes first.

4.3. Treatments

Subjects will be randomized to one of two treatment groups:

- **LMWH/Edoxaban group**: Therapeutic doses of LMWH (SC) will be administered for at least 5 days; this 5-day period may include the pre-randomization LMWH (if applicable). The choice of this parenteral LMWH is up to the treating physician. Thereafter, edoxaban will be started orally at 60 mg QD (2 × 30 mg tablets; 30 mg QD for subjects requiring dose adjustment) for the remainder of the treatment period.
- **Dalteparin group**: After randomization, dalteparin will be administered at a dose of 200 IU/kg SC (maximum daily dose 18,000 IU) for 30 days. The 30 day period may include the pre-randomization anticoagulant treatment if dalteparin

was used in therapeutic doses. Thereafter (approximately Day 31 forward), dalteparin will be administered at a dose of 150 IU/kg SC (~ 75% - 83% of the initial dose) for the remainder of the treatment period.

The edoxaban daily dose should be decreased to 30 mg QD for:

- body weight ≤ 60 kg; or
- creatinine clearance [CrCL] between 30 and 50 mL/min inclusive;
- concomitant use of P-gp inhibitors (eg, hormonal agents: tamoxifen, enzalutamide, abiraterone).

Dose reduction of edoxaban to 30 mg QD is intended only during concomitant use of P-gp inhibitors. When use of these inhibitors is discontinued/intermittent (eg, between chemotherapy cycles) full 60 mg edoxaban dose should be used.

After randomization, if the subject's CrCL becomes ≤ 50 mL/min and ≥ 30 mL/min and the decrease in CrCL is > 20% from the subject's baseline CrCL value, repeat the measurement preferably within 1 week. If the repeat measurement confirms this decrease, the edoxaban dosage regimen will be reduced permanently, even if the subject subsequently experiences improved CrCL to > 50 mL/min at a later measurement.

After randomization, if the subject's body weight drops to ≤ 60 kg (confirmed by repeat measurement at least 1 week apart) and the body weight change is > 10% of the subject's baseline body weight, the edoxaban dosage regimen will be reduced permanently, even if the subject subsequently re-gains weight to > 60 kg.

4.4. Blinding

This study has an open-label, blinded-evaluator design. The subjects, Investigators, Sponsor, Contract Research Organization (CRO), and Academic Research Organization (ARO) staff involved in the treatment or clinical evaluation of the subjects will be aware of the treatments received.

An independent Clinical Events Committee (CEC) will adjudicate and categorize the presenting index diagnosis, VTE outcomes, cardiovascular events, bleeding events, selected hepatic events, and death. Adjudicators will be blinded as to subject treatment allocation.

There will be an independent Data Monitoring Committee (DMC) to periodically review and examine the safety and efficacy data (mortality and events, bleeding events, serious adverse events [SAEs], systemic embolic event [SEE]).

The specifications for generation of the randomization schedule will be prepared by the CRO in charge of the IXRS. For this study, the randomization schedule refers to a list that includes the randomization number, randomization block number, and treatment.

4.5. Determination of Sample Size

Assuming a hazard ratio of 1, a total of 191 overall primary events are projected to accrue in the mITT analysis set which will ensure at least 80% power for the primary analysis at a non-inferiority margin for the hazard ratio of 1.5 and a Type I error of 0.05 (two-sided).

Assuming a primary combined outcome rate (recurrent VTE or major bleed) of 20.0%, a total of 1000 subjects are expected to be randomized to study treatment in order to accrue 191 overall primary events in the mITT analysis set.

5. EFFICACY AND SAFETY ENDPOINTS

5.1. Primary Outcome Endpoint

The primary outcome endpoint is the composite of recurrent VTE, or major bleeding.

Recurrent VTE is either:

- symptomatic confirmed (new) DVT or (new) PE;
- unsuspected (new) proximal DVT, which is a DVT coincidentally detected during other investigations (eg, abdominal or pelvic CT for cancer staging). This DVT will only be included as an outcome if it concerns a (new) clot located in the popliteal or more proximal leg veins. A thrombus detected in the IVC or iliac veins on an abdominal or pelvic CT does not require additional confirmation. A thrombus detected in the common femoral vein or more distal veins can only be confirmed if CUS (or venography) diagnostic criteria are also met.
- unsuspected (new) PE, which is an embolism coincidentally detected during other investigations (eg, CT for cancer staging), that involves segmental or more proximal pulmonary arteries.
- fatal PE (including unexplained death for which PE cannot be ruled out).

Major bleeding is defined as overt bleeding and:

- associated with a decrease in hemoglobin of $\geq$ 2 g/dL, or
- leading to a transfusion of $\geq$ 2 units of packed red blood cells or whole blood, or
- occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- contributing to death.

All suspected recurrent VTE and bleeding events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

5.2. Secondary Efficacy Endpoint

The secondary endpoints include:

- Recurrent VTE
- Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE-related death;

- Recurrent deep vein thrombosis (DVT);
- Recurrent pulmonary embolism (PE);

All suspected VTE events, deaths, and bleeding events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

5.3. Safety Endpoints

The primary safety endpoint is major bleeding, and the secondary safety endpoints include the following:

- Major + clinically relevant non-major bleeding;
- Clinically relevant non-major bleeding;
- All bleeding;
- Mortality from all causes.

CEC adjudication results will form the basis for the final analysis. Healthcare resource utilization for potential recurrent VTE and bleed events will also be analyzed.

5.4. Exploratory Safety Endpoint

Exploratory endpoints include:

- CV events (MI, stroke, SEE);
- Thrombotic events at other locations;
- Reason for permanent early discontinuation of study drug.

All suspected CV events and other thrombotic events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

5.5. Drug Concentration, Pharmacodynamic, and Pharmacogenomic Measurements

Not applicable.

6. STATISTICAL METHODS

The data analysis will be performed by Quintiles under the guidance of the sponsor study biostatisticians. SAS version 8.2[1,2,3] or newer will be used in the statistical analysis.

All data will be organized and analyzed according to the scheduled times as outlined in the protocol and by visit as denoted on the Electronic Case Report Form (eCRF).

The clinical database is the source for data used in analyses. The primary data source contains all data (including local laboratory data) reported in the Electronic Data Capture (eDC) database. Other sources of data used in analyses are:

- Event adjudication data from CEC
- Randomization data collected from IXRS including the stratification information.
- Post randomization dose adjustment information from IXRS.

All suspected and reported primary, secondary and exploratory endpoint events are captured on the eCRF . All endpoint events reported on the event forms will be adjudicated in a blinded manner by the CEC. The CEC adjudicator's results will be entered into the adjudication database separate from eDC database. The final analyses will be performed based on the CEC's adjudicated outcomes. Investigator reported events will also be summarized.

6.1. General Procedures and Data Presentation

Raw data will be presented with the exact precision (decimal points) with which it was collected. The number of decimal places to display for calculated data will be determined by the scale of the measurement. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when all calculated values are within the interval (10, 100), with 10 being inclusive; 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.

For continuous variables, statistical summaries will include means, medians, standard deviations, maximums, and minimums. Means and medians will be displayed to one more decimal places than the raw or calculated data; standard deviations and other dispersion statistics will have two more decimal places; and minimums and maximums will be displayed to the same number of decimal places as the raw or calculated data.

For categorical variables, statistical summaries will include counts and percentages. Percentages will be reported with exactly one decimal place. In general, percentages are based on the total number of subjects on whom information is available within the analysis set of interest and in that treatment group. For AEs and incidence analyses, percentages are based on the total number of subjects in the analysis set of interest and in that treatment group.

Kaplan-Meier survival curves will be presented for all time to event analyses.

All tests and CIs are 2-sided unless specified otherwise.

All p-values will be displayed with four decimal places.

All by visit summaries and analyses will use scheduled nominal visit; if two or more visits have same nominal visit, the first one will be used.

6.2. Adjustments for Covariates

For the primary outcome variable, the time to first event will be analyzed using the Cox proportional hazards model with model terms for treatment group and the following randomization stratification factors:

- Bleeding Risk (Yes; No)
- Need for dose adjustment (Yes; No)

Secondary efficacy and key safety endpoints will be analyzed using the similar Cox proportional hazards model with model terms for treatment group and the same covariates.

6.3. Handling of Dropouts or Missing Data

All analyses will be performed on observed data only and no missing data will be imputed unless otherwise described in the analysis sections. Right censoring will apply for all time to event analyses.

6.3.1. Partial and Estimated Dates

Partial and estimated dates are allowed for some of the date fields as collected on the eCRF. Partial dates will be imputed differently depending on whether the date is, by nature, a baseline date (e.g., the diagnosis date of a medical history) or a post-baseline date (e.g., the onset date of an AE). Estimated dates will be used as collected. In general, a conservative imputation rule will be implemented for all partial dates that will either include more events or result in events being considered part of the On-Treatment Period (i.e., while on study drug or within three days of last dose of study drug).

6.4. Interim Analyses

No formal interim analysis is planned; however, risk-benefit will be evaluated by the DMC and the DMC chairman will alert the chairman of the Steering Management Coordinating Committee (SMCC) in the event of any clinically concerning safety issues.

Access to the DMC tabular risk benefit data will be restricted to DMC members. The procedures of the DMC are described in its charter.

6.5. Data Monitoring Committee (DMC)

An independent DMC will monitor safety during the study and give recommendations to the SMCC. This committee will be unblinded to subjects' treatment groups. The primary role for the DMC will be to examine the unblinded safety and efficacy data (VTE events, bleeding events, deaths, MIs, stroke, SEE, thrombotic events at other locations, liver enzyme and bilirubin abnormalities, SAEs) in an ongoing manner and alert the Chairman of the SMCC in the event of any clinically concerning safety issues. See the submitted DMC charter for details.

6.6. Clinical Events Committee (CEC)

A CEC will objectively (blinded) adjudicate and categorize the presenting index diagnosis, protocol specified VTE events, bleeding events, deaths, CV events (MI, stroke, SEE), thrombotic events at other locations, selected hepatic dysfunction / liver enzyme elevation. Due to logistical constraints, adjudication of index events will be performed after randomization; hence, these adjudicated index events will not be used to qualify the subject for study, but rather to subsequently define the efficacy analyses sets. Final adjudicated results from the CEC assessments will be recorded in the adjudication database separate from eDC database for final analysis. See the submitted CEC charter for details.

6.7. Data Pooling

No Data pooling is planned for this study.

Summary statistics for key efficacy and safety variables will be provided by region/country.

Region	**Countries**
North America	USA, Canada
Central Europe	Czech Republic, Hungary
South Europe	France, Italy, Spain
Western Europe	Austria, Belgium, Germany, The Netherlands
Australia-New Zealand	Australia, New Zealand

6.8. Multiple Comparisons/Multiplicity

The following test plan will be followed in the efficacy and safety analyses:

Step 1: Test the primary outcome endpoint (overall recurrent VTE or major bleeding) based on the Modified Intent-to-Treat (mITT) Analysis Set for non-inferiority at α=0.05.

Step 2: If non-inferiority is achieved in step 1, then test the primary outcome endpoint (overall recurrent VTE or major bleeding) based on the mITT Analysis Set for superiority at α=0.05.

Step 3: Test the primary safety endpoint (on-treatment major bleeding) based on the Safety Analysis Set for superiority at α=0.05.

7. STATISTICAL ANALYSIS

7.1. Analysis Sets

Randomized Analysis Set: All subjects randomized to treatment.

Modified Intent-to-Treat (mITT) Analysis Set: All randomized subjects who receive at least one dose of post-randomization study drug.

Per Protocol (PP) Analysis Set: All randomized subjects who receive at least one dose of study drug, who have not experienced treatment misallocation, and for whom the index Deep Vein Thrombosis (DVT) or pulmonary embolism (PE) event at baseline was confirmed by the CEC. Treatment misallocation is defined as a patient taking incorrect treatment during the entire study period.

Safety Analysis Set: All randomized subjects who receive at least one dose of study drug.

Frequency for each analysis set will be summarized by treatment group for all subjects randomized.

7.2. Disposition of Subjects

Enrollment summary will be presented by region, country and treatment group for all subjects randomized.

Disposition of subjects will be summarized for each analysis set by treatment group for the Safety/mITT Analysis Set. This summary includes the total number of subjects completing the study per protocol**,** completing treatment (all subjects who permanently stop study treatment at a protocol defined stopping point), discontinuing from treatment, and discontinuing from the study. Reasons for discontinuation from treatment and discontinuation from the study will be provided. A comparison by the treatment group will also be performed for total number of subjects completing the study and for those discontinuing the study.

A summary of study drug discontinuation/interruptions will include, but not be limited to, the following: number and percent of subjects permanently discontinuing study drug and reason, number and percent of subjects with at least one interruption and reason, and number and percent of occurrences of study drug interruptions (1, ≥2 occurrences) for the Safety/mITT Analysis Set.

Overall study period duration will be summarized for the Safety/mITT Analysis Set. Time to premature discontinuation from study by treatment group will be displayed graphically for the Safety/mITT Analysis Set.

Listings will be provided for reasons for study discontinuation and study drug discontinuation separately.

7.3. Protocol Deviations

A descriptive summary and listing of all subjects with major protocol deviations will be provided for the mITT Analysis Set. Prior to database lock, review will occur to finalize the list of subjects who meet the criteria for major protocol deviations.

Major protocol deviations are:

- Unconfirmed cancer, unconfirmed history of cancer or basal-cell or squamous-cell carcinoma of the skin
- Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of DVT and/or PE;
- More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, unfractionated heparin, and fondaparinux per local labeling), oral direct anticoagulants or VKA prior to randomization to treat the current (index) episode;
- Treatment with therapeutic doses of an anticoagulant other than that used for pre-treatment of the current (index) VTE episode prior to randomization;
- Treatment misallocation;

- Concomitant use of disallowed medications (e.g., concomitant anticoagulation therapy) that impact the evaluation of primary outcomes for efficacy and safety;
- CrCL < 30 mL/min or Platelets < 50,000 cc^3 at the time of randomization.

Any site for which subject data authenticity is suspect and cannot be confirmed will be identified at a data review meeting and subsequently excluded from all efficacy and safety analyses. Any such decisions will be finalized and recorded prior to database lock. A listing will also be provided to summarize subjects with major protocol deviations.

7.4. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and by Dose Adjustment Status at Randomization for the Safety/mITT Analysis Set. All categorical parameters will be summarized by frequency and percentage based on the number of subjects with available data for that parameter. Variables such as age, body weight, BMI, and CrCL will also be summarized by descriptive statistics including means, medians, standard deviations, maximums, and minimums.

The following categorical baseline characteristics derived from IXRS will be presented:

- Bleeding risk (yes, no);
- Body Weight (≤60.0 kg, >60.0 kg);
- Creatinine clearance (≥30-≤50 mL/min, >50 mL/min);
- P-gp use at randomization (yes, no);
- Dose adjusted at randomization (yes, no).

Other categorical baseline characteristics will include:

- Age (<65, ≥65-<75, ≥75 years);
- Gender
- Race
- Ethnicity (Hispanic/Latino vs Not) for USA subjects only
- Presenting diagnosis of DVT or PE
- ECOG performance status
- Primary cancer history/ Active cancer (specified in protocol section 6.1)
- Past medical history
- Region/country

7.5. Measurements of Treatment Compliance

Study drug dosing compliance will be summarized for the Safety/mITT Analysis Sets and will be presented by the three categories: <80%, ≥80% and ≤ 120%, as well as >120% of doses taken.

Edoxaban compliance over the whole treatment period will be calculated as

*(total number of edoxaban tablets taken)/ (total number of edoxaban tablets should be taken)*100*

Total number of edoxaban tablets taken will be calculated as:

$\sum$*(amount of dispensed at previous visit – amount of returned at current visit)*

Total number of edoxaban tablets that should be taken will be calculated as:

$\sum$*tablets * (days between two visits – planned interruption days)*

For 60 mg dose, 2 tablets are to be taken; 1 tablet to be taken for 30 mg dose.

Treatment compliance for dalteparin will be calculated using the same method but will be accounting for number of dalteparin syringes instead of number of edoxaban tablets.

7.6. Extent of Exposure to Study Drug

Subject exposure will be summarized for the Safety/mITT Analysis Sets and will be presented by total time on study drug at 3 months (>=85 days), 6 months (>=175 days) and 12 months (>=353 days) after the first study drug dose. Descriptive statistics, including mean, median, standard deviation, maximum, and minimum, will also be provided for total time on study drug, duration of exposure.

Total time on study drug (exposed to study drug) is defined as the total number of days the subject took study drug, with interruptions not included in the interval of time. For each subject, the total time on study drug may actually be a few days less than the total time in all On-Treatment Periods as it does not include the three days after last dose of study medication.

Total treatment period is defined as the total number of days the subject took study drug, with interruptions included in the interval of time (date of last study dose – date of first study dose +1).

Descriptive statistics by treatment group will also be provided for intended treatment duration as collected on the eCRF.

Number of subjects exposed to anti-coagulation therapy prior to randomization will be summarized for the Safety/mITT Analysis Set by treatment groups as: [LMW] heparin or other anti-coagulation use within the 5 days prior to randomization: None, have been used for ≤ 5 days, and have been used for > 5 days.

7.6.1. Targeted Cancer Therapy

Targeted cancer therapy received on or after initial dose of study drug will be summarized by treatment group for the Overall Study Period and the Safety/mITT Analysis Set.

7.6.2. Concomitant Medications

Targeted and non-targeted concomitant medications taken on or after initial dose of study drug will be summarized separately by treatment group for the Overall Study Period. Medications will be coded using the World Health Organization (WHO) drug dictionary 01June2010 Version or later. Safety/mITT Analysis Set will be used for this analysis.

7.6.3. Non-Drug Therapies

Non-drug therapies performed on or after the initial dose of study drug will be summarized by treatment group for the Overall Study Period. Safety/mITT Analysis Set will be used for this analysis.

7.7. Analysis of Primary Outcome and Efficacy

The following will be applied to all efficacy analyses where applicable.

The mITT and Per Protocol Analysis Sets will be used in the analysis of primary outcome and all efficacy endpoints. Analyses for all efficacy endpoints will be based on the randomized treatment even if a subject inadvertently receives the incorrect study drug. Endpoints will be summarized by treatment group unless otherwise stated.

The summary statistics for the primary outcome and efficacy endpoints and their individual components will be provided. These statistics include the number of first events (i.e., the number of subjects with the event). For primary outcome and secondary efficacy endpoints, the hazard ratios of the LMWH/edoxaban versus dalteparin with 95% CIs will be provided using the Cox proportional hazards model with model terms for treatment and the randomization stratification factors (bleeding risk, and need for dose adjustment) as covariates. Kaplan-Meier plots[4] of time to events for the endpoint will also be provided by treatment group. CEC adjudication results will be the basis for the primary analysis.

The reference date for efficacy analysis during Overall Study Period will be the randomization date. The reference date analysis during On-Treatment Period will be the first dose date.

Incidence rates of subjects with ≥ 1 events, ≥ 2 events, etc will be analyzed for each of the key efficacy endpoints.

7.7.1. Adjudicated Efficacy Endpoint Derivations

The detailed definition for each endpoint event is described in the submitted CEC Charter.

7.7.2. Analyses of Primary Outcome and Efficacy Endpoints

7.7.2.1. Analyses of the Primary Outcome Endpoint

7.7.2.1.1. Primary Analysis of the Primary Outcome Endpoint

The primary analysis will compare treatment efficacy for the occurrence of adjudicated composite primary outcome endpoint (recurrent VTE [symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, unsuspected PE, fatal-PE] or major bleed) using the Overall Study Period for all subjects in the mITT Analysis Set. The events that will be counted in this analysis are those events occur from the date of randomization through the end of the 12-month (Day 365) study period, the last available date that the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global EOT, regardless of whether the subject was taking study drug, whichever comes first.

For subjects who do not experience an event, the time to first event will be censored at Day 365, or the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global EOT, whichever comes first. Subjects lost to follow-up, subjects who died because of reasons other than DVT/PE, or subjects who withdrew informed consent before the end of the 12-month treatment period and who did not have a primary outcome, will be censored at the last day the subject had a complete assessment for study outcomes.

The primary outcome analysis is designed to demonstrate that the LMWH/edoxaban Group is non-inferior to the dalteparin Group at a non-inferiority margin of 1.5 for hazard ratio, using a significance level of α=0.05. The time to first event will be analyzed using a Cox proportional hazards model including model terms for treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates. If the upper limit of the two-sided 95% CI of the hazard ratio is below 1.5, then non-inferiority to dalteparin Group will be considered established for the LMWH/edoxaban Group.

The assumptions of proportional hazards will be investigated graphically (e.g., log (-log)-plots and plots of scaled Schoenfeld residuals) for the primary analysis. If serious violations occur, then a logistic model including model terms for treatment, and the randomization stratification factors as covariates will be used. The impact of selected baseline covariates on the primary outcome will be described by calculating adjusted Hazard Ratios and corresponding 95% CI of the treatment effect.

The components of primary outcome endpoint (recurrent VTE [symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, unsuspected PE, fatal-PE] or major bleed) for each treatment group will be summarized.

A listing of suspected endpoints and their adjudicated results will be provided.

7.7.2.1.2. Sensitivity Analyses of the Primary Outcome Endpoint

The following sensitivity analyses will be performed for the Primary Outcome Endpoint:

- On-Treatment events based on the PP Analysis Set will be analyzed using the counting process approach of the Cox proportional hazards regression model including treatment group, and the stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates. An On-Treatment event is defined as the event occurring during the time period the subject is taking study drug up to 3 days after their last dose for that time period. Only events occurring prior to or on Day 365 will be included into this analysis. Subjects who do not experience an On-Treatment event will be censored at Day 365, or the time study drug is permanently discontinued plus 3 days or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global EOT, whichever comes first.
- Events occurring during the first 6 months (180 days) based on the mITT Analysis Set will be analyzed using the same statistical model as the analysis of primary outcome during the Overall Study Period. The time to event is defined as the time (days) from the randomization to the first event during the first 6 months (until Day 180) after randomization. Subjects who do not experience an event until Day 180 will be censored at Day 180, or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, whichever comes first.
- The same analyses for primary outcome endpoint based on the mITT Analysis Set during Overall Study Period, and the mITT Analysis Set during the first 6 months study period, will also be carried out by dose adjustment status at randomization.

7.7.2.1.3. Superiority Analysis of the Primary Outcome Endpoint

If non-inferiority in the primary outcome is established, LMWH/edoxaban will be compared to dalteparin for superiority (α=0.05, two-sided) with regard to the time to an event in the composite clinical outcome of recurrent VTE or major bleed during the 12-month study period. This analysis will be based on the mITT Analysis Set during the Overall Study Period using the same proportional hazard model as for the primary outcome. The same analysis will also be carried out using the same proportional hazard model with counting process for the On-Treatment Period for the Per Protocol Analysis Set.

7.7.2.2. Analysis of the Secondary Efficacy Endpoint

Analysis for the secondary efficacy endpoints will be performed using the Overall Study Period for the mITT Analysis Set using Cox proportional hazards model including model terms for treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates. Descriptive summaries will also be provided. Secondary efficacy endpoints include:

- recurrent VTE;
- event-free survival: the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE -related death;
- recurrent DVT;
- recurrent PE.

The same event inclusion and censoring method used in primary outcome endpoint will be applied to secondary efficacy endpoints. The LMWH/edoxaban will be compared to dalteparin for superiority (α=0.05, two-sided) with regard to the time to an event in recurrent VTE during the Overall Study Period.

Same sensitivity analyses used in primary outcome analysis will also be applied to secondary efficacy endpoints, which include:

- Events occurring during the first 6 months (180 days) based on the mITT Analysis Set using the Initial 6-Month Study Period.

7.7.2.3. Subgroup Analyses for the Primary Outcome and Secondary Efficacy Endpoints

Subgroup analyses will be performed for the primary outcome and secondary efficacy endpoints using the Overall Study Period approach for the mITT Analysis Set, and the Initial 6-Month Study Period for the mITT Analysis Set. Descriptive summaries will be provided. The percentages will be based on the total number of subjects that make up the subgroup being summarized, regardless if an event occurred**.** Forest plots will be generated for subgroup analyses.

Subgroups will be based on characteristics including, but not limited to, the following:

1. Presenting diagnosis of DVT or PE. Adjudicated results will form the basis for the subgroup analysis. In the instance the CEC is unable to confirm the diagnosis, the investigators' diagnosis will be used).
2. Age (<65 years vs. ≥65 years, <75 years vs. ≥75 years)
3. Gender (male vs. female)
4. Bleeding Risk at randomization (Yes/No)
5. Dose adjustment at randomization, (dose adjusted: Yes/No)
6. CrCL at randomization: 30-<60, 60-<90, >=90 mL/min
7. Platelet at randomization: 50,000-100,000/mL vs > 100,000/mL
8. P-gp use at randomization (Yes, No)
9. Race
10. Baseline ECOG Performance Status
11. Initial heparin treatment duration on or after randomization (for example, <5 days, 5-7 days, 8-10 days, >10 days; ≤median, >median; ≤25^{th} percentile, >25^{th}-50^{th} percentile, >50^{th}-75^{th} percentile, >75^{th} percentile). The categorical groups will be determined based on subjects in each category prior to database lock.
12. Heparin use prior to randomization (Yes/No)
13. Active cancer at randomization (Yes/No)

The incidence of VTE based on each subgroup will be estimated and a 95% CI for the LMWH /edoxaban: dalteparin hazard ratio will be constructed.

7.7.2.4. Exploratory Efficacy Analyses

The impact of baseline covariates on the primary outcome will also be described by calculating adjusted hazard ratios and corresponding 95% CIs for the treatment effect.

The investigator reported events for primary and secondary endpoints will be summarized using Overall Study Period approach for the mITT analysis set.

Summary of agreement between investigator and adjudicator for investigator suspected, confirmed and CEC confirmed primary and secondary efficacy endpoints will be provided by treatment group for the mITT Analysis Set.

7.8. Analysis of Safety

The following procedures will be applied to all safety endpoints unless otherwise stated in the individual sections.

Safety analyses will be summarized for all subjects included in the Safety Analysis Set by treatment group. Analyses for all safety endpoints will be based on randomized treatment, unless a subject inadvertently receives the incorrect study drug during the entire study, in which case, the subject will be grouped according to the treatment actually received. The time periods used for analyses are described for each safety parameter. Adjudicated safety events along with select key investigator reported safety events will be analyzed. All remaining safety results will be summarized descriptively.

7.8.1. Safety Event Derivations

Detailed definitions for bleeding categories are described in the submitted CEC Charter.

7.8.1.1. Analysis of the Primary and Secondary Safety Endpoints

The primary safety endpoint is major bleeding events that occur during On-Treatment Period (on study drug or up to 3 days after the last dose for that time period.)

The time from date of initial study dose to first major bleeding will be compared between treatment groups for superiority (α=0.05 two-sided) for subjects in the Safety Analysis Set, using a Cox's proportional hazard regression model with counting process using the model terms for treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates.

For subjects did not experience any event, they will be censored 3 days after the day of permanent study medication discontinuation, the last day the subject had a complete assessment for study outcomes, or the day of global EOT, whichever comes first.

Subjects who experience multiple major bleeding events will be summarized by treatment groups.

Incidence and Hazard Ratio (with 95% CI) for the following secondary safety outcomes will be calculated based on the Safety Analysis Set and On-Treatment-approach using the Cox proportional hazards regression model with counting process approach with the model terms for treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates:

- Clinically relevant non-major bleeding
- Major + clinically relevant non-major bleeding
- All bleeding

Adjudicated bleeding events will also be summarized by category, location, characteristics, and circumstance as recorded in the CRF for major bleeding, clinically

relevant non-major bleeds, and major plus clinically relevant non-major bleeds. All investigators reported bleeds will be summarized separately from adjudicated bleeds.

Adjudicated death events occurred during Overall Study Period described above will also be analyzed using a Cox's proportional hazard regression model with the treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates for subjects in the Safety Analysis Set. Subjects will be censored after the last day the subject had complete assessment (in-person visit or by telephone) for study outcomes, or the day of global EOT, whichever comes first.

A listing of suspected endpoints and their adjudicated results will be provided.

7.8.1.2. Healthcare Resources Utilization

The incidence of hospital admission related to recurrent VTE or bleeding events will be summarized by treatment group for the Safety Analysis Set using the Overall Study Period. Total number of days in hospital, intensive care unit, step-down ward and general hospital ward will be descriptively summarized.

7.8.1.3. Exploratory Safety Endpoints

Incidence and Hazard Ratio (with 95% CI) will be calculated based on the Safety Analysis Set and On-Treatment-approach using the Cox proportional hazards regression model with counting process and with the model terms for treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates.

The exploratory safety endpoints include:

- CV events (MI, stroke, SEE)
- Thrombotic events at other locations.

Exploratory safety endpoints occurred during the Overall Study Period described above will also be analyzed for subjects in the Safety Analysis Set.

The investigator reported endpoints will be summarized separately for the On-Treatment Period and Overall Study Period.

Summary of agreement between investigator and adjudicator for investigator suspected, confirmed and CEC confirmed safety endpoints will be provided by treatment group for the Safety Analysis Set.

7.8.1.4. Subgroup Analyses for the Primary and Secondary Safety Endpoint

Subgroup analyses will be performed for the adjudicated major bleeding, major or CRNM bleeding using the Safety Analysis Set for the On-Treatment Period. Descriptive summaries will be provided. Percentages will be based on the total number of subjects that make up the subgroup being summarized, regardless if an event occurred**.** Forest plots will be generated for subgroup analyses. No inferential analysis will be conducted unless specified otherwise. Subgroups to be used for safety analysis will be the same as those for efficacy analysis.

7.8.2. Liver Enzyme and Bilirubin Abnormalities

Liver enzyme and bilirubin abnormalities will be summarized by treatment group using the On-Treatment Period for the Safety Analysis Set. These summaries will be for based on the adjudicated data, the investigator reported data, and the local laboratory data. In addition, subject listings will be presented for those subjects with reported abnormalities whose cases are sent to adjudicators.

Based on the adjudication information completed by the adjudicators, the nature, clinical severity, and causality of an event and whether Hy's law was satisfied will be presented. The number of subjects adjudicated as having hepatocellular injury will be summarized.

Furthermore, regardless of the investigator reports, all local laboratory results will be evaluated by treatment group for the incidence of elevated liver enzymes for the Safety Analysis set during the On-Treatment Period. The number and percentage of subjects with elevation of liver enzymes according to various multiples of Upper Limit of Normal (ULN) (Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) ≥3xULN, ≥5xULN, ≥8xULN, ≥10xULN, ≥20xULN; total bilirubin ≥1.5xULN, ≥2xULN, ≥3xULN, ≥5xULN) will be summarized by treatment group. A combination of ALT and/or AST ≥ 3xULN accompanied by concurrent (within 37 days after the maximum AST/ALT) total bilirubin ≥ 2xULN will be summarized. Incidence of Alkaline Phosphatase (ALP) will be summarized using cutoffs of 1.5xULN, ≥ 2xULN, 3xULN, as well as confirmed elevation using these same boundaries. Additional combinations of (ALT and/or AST ≥ 3xULN accompanied by concurrent total bilirubin ≥ 2xULN and ALP ≥ 2xULN) and (ALT and/or AST ≥ 3xULN accompanied by concurrent total bilirubin ≥ 2xULN and concurrent ALP < 2x ULN) will be presented and analyzed. For laboratory data, the assessments performed prior to or on the first dose date will be excluded. A listing with clinically significant abnormal values for these tests will be provided.
Scatter plots of Peak AST/ALT vs. Peak Total Bilirubin will be displayed for the Overall Study Period. A separated scatter plot of Peak AST/ALT vs. Peak Total Bilirubin after starting Edoxaban will be displayed (i.e., AT and TBL values obtained 1 day after starting edoxaban).

7.8.3. Adverse Events

Two sets of AE summaries will be presented:

1. All AEs excluding investigator confirmed VTE, bleeding, MI, Stroke, SEE, and thrombotic events.
2. For all investigator confirmed VTE, bleeding, MI, Stroke, SEE, and thrombotic events.

All adverse event (AE) summaries will be presented by System Organ Class (SOC) and by Preferred Term (PT) within each SOC as classified by the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary[5] Version 12.0 or newer.

The primary Treatment-emergent Adverse Event (TEAE) analyses will be presented using the On-Treatment Period for the Safety Analysis Set. TEAEs are defined as an event that emerge during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state.

An overall incidence summary of AEs with corresponding 95% CIs for incidence rates will be provided, which includes the following:

- Number and percent of subjects with at least one Treatment-emergent Serious Adverse Event (TESAE).
- Number and percent of subjects with at least one TEAE.
- Number and percent of subjects with at least one drug-related TEAE.
- Number and percent of subjects with at least one TEAE with fatal outcome.
- Number and percent of subjects with at least one TEAE that caused study drug permanent discontinuation.

This summary will also be presented for all AEs including investigator confirmed VTE, bleeding, MI, Stroke, SEE, and thrombotic events.

Incidence rates by SOC and PT will be presented by treatment group for the following:

- TEAEs/ TESAEs
- Drug-related TEAEs (only for AEs excluding investigator confirmed events)
- TEAEs by maximum severity (only for AEs excluding investigator confirmed events)
- TEAEs with fatal outcome
- TEAEs/TESAEs that caused study drug permanent discontinuation

SAEs that occurred prior to the initial dose of study drug will be presented in a subject listing. Any AEs leading to death or permanent discontinuation of study drug will also be presented in a subject listing. Investigator confirmed major bleeding AEs, deaths, and special interest AEs will be presented in subject listings separately as well.

7.8.4. Clinical Laboratory Evaluations

The clinical laboratory evaluations at each scheduled visit and the change from baseline will be summarized for the Safety Analysis Set by treatment group. Shift from baseline with specific clinically meaningful ranges for select clinical local laboratory evaluations will be summarized by treatment group. This will be summarized at each scheduled visit, last assessment and at the worst assessment. If a laboratory retest occurs within a day, then the later value will be used for summarization.
The number and percentage of subjects with clinically relevant abnormal laboratory values will be calculated for each treatment group for selected laboratory parameters. Percentages for these summaries will be based on the available data, rather than the total number of subjects.

7.8.5. Vital Signs and Physical Exam

Observed values of vital signs including systolic and diastolic blood pressure (mmHg), pulse (bpm), weight (kg) and height (cm) collected at randomization will be summarized. Observed and changed from baseline in weight collected at each scheduled visit will also be summarized.

Clinically significant physical examination findings will be listed by treatment group for each body system.

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[4] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.

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The International Federation of Pharmaceutical Manufacturers Association (IFPMA), International Committee on Harmonization, Geneva, Switzerland, 2001.

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STATISTICAL ANALYSIS PLAN

A PHASE 3B, PROSPECTIVE, RANDOMIZED, OPEN-LABEL, BLIND EVALUATOR (PROBE) STUDY EVALUATING THE EFFICACY AND SAFETY OF LOW MOLECULAR WEIGHT HEPARIN (LMWH)/EDOXABAN VERSUS DALTEPARIN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

Protocol Number: DU176b-D-U311

- **Version 3.0, 02 October 2017**

DAIICHI SANKYO PHARMA DEVELOPMENT

Authorization Signature Page

A PHASE 3B, PROSPECTIVE, RANDOMIZED, OPEN-LABEL, BLIND EVALUATOR (PROBE) STUDY EVALUATING THE EFFICACY AND SAFETY OF LOW MOLECULAR WEIGHT HEPARIN (LMWH)/EDOXABAN VERSUS DALTEPARIN IN VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

Authors:

20Oct2017
Date

George Zhang, Ph.D.
Director, Biostatistics
Daiichi Sankyo Pharma Development

2 Oct 2017
Date

Christine Lui, M.S.
Statistical Scientist
Quintiles, Inc.

Approved by:

20Oct2017
Date

Joshua Betcher, Ph.D.
Senior Director, Biostatistics
Quintiles, Inc.

20Oct2017
Date

Minggao Shi, Ph.D.
Executive Director, Biostatistics
Daiichi Sankyo Pharma Development

- **Regulatory History**

Date	Communication

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1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

1.1. Abbreviations

AEs	Adverse Events	Kg	Kilogram
ALP	Alkaline Phosphatase	Mg	Milligram
ALT	Alanine Aminotransferase	min	Minute
AST	Aspartate Aminotransferase	mITT	Modified Intent-to-Treat
ARO	Academic Research Organization	PE	Pulmonary Embolism
CEC	Clinical Events Committee	PK	Pharmacokinetic
CI	Confidence Interval	PROBE	Prospective, randomized, open-label, blind-evaluator (study design)
CrCL	Creatinine Clearance	PT	Preferred Term
CRO	Contract Research Organization	qd	Once daily
CV	Cardiovascular	SAE	Serious Adverse Event
DMC	Data Monitoring Committee	SEE	Systemic Embolic Event
DSPD	Daiichi Sankyo Pharma Development	SI	Standard International
DVT	Deep Vein Thrombosis	SOC	System Organ Class
eCRF	Electronic Case Report Form	TEAE	Treatment-emergent Adverse Event
eDC	Electronic Data Capture	TESAE	Treatment-emergent Serious Adverse Event
IXRS	Interactive Voice/Web Response System	ULN	Upper Limit of Normal
LMW	Low Molecular Weight	VTE	Venous Thromboembolic Event
MI	Myocardial Infarction	WHO	World Health Organization
MedDRA	Medical Dictionary for Regulatory Activities		

1.2. Definition of Terms

Study Drugs: initial Low Molecular Weight Heparin (LMWH) (dosed after randomization), edoxaban, and dalteparin.

Treatment Groups: References within this Statistical Analysis Plan (SAP) to the "LMWH/edoxaban Group" represent those subjects receiving initial Low Molecular Weight Heparin followed by edoxaban. References to the "dalteparin" represent those subjects receiving dalteparin.

Overall Study Period: The time from the randomization date to the last study follow up visit.

Initial 6-Month Study Period: The time from the randomization date to Day 180, or the last study follow up visit, whichever comes first.

On-Treatment Period: The time period the subject is taking study drug up to 3 days after their last dose for that time period. A subject may have multiple periods of drug use if they temporarily interrupt and resume study drug during the study.

Initial 6-Month On-Treatment Period: The time period the subject is taking study drug up to 3 days after their last dose or up to Day 180, whichever comes first.

2. INTRODUCTION

This Statistical Analysis Plan (SAP) document provides a more technical and detailed description of the statistical analyses as outlined and/or specified in the study protocol Version 3.0 (dated 20 January, 2016).

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is to demonstrate the non-inferiority of edoxaban (preceded by a short course of LMWH) compared with dalteparin for the prevention of the combined outcome of recurrent venous thromboembolism (VTE) or major bleeding in subjects with VTE associated with cancer during a 12-month study period. The LMWH/edoxaban will be considered non-inferior to dalteparin if the upper limit of the two-sided 95% confidence interval (CI) for the hazard ratio is less than 1.5. If non-inferiority is established, LMWH/edoxaban will be compared with dalteparin for superiority.

3.2. Secondary Objectives

The secondary objectives are to compare LMWH/edoxaban to dalteparin with regard to rates of the following endpoints during the 12-month study period:

- Recurrent VTE
- Major Bleeding
- Clinically relevant non-major (CRNM) bleeding;
- Major + CRNM bleeding;
- All Bleeding;
- Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE-related death;
- Mortality from all causes;
- Recurrent deep vein thrombosis (DVT);
- Recurrent pulmonary embolism (PE);
- Healthcare resource utilization for potential recurrent VTE and bleed events.

3.3. Exploratory Objectives

Exploratory objectives include comparing LMWH/edoxaban to dalteparin with regards to:

- Cardiovascular (CV) events (myocardial infarction (MI), stroke, systemic embolic event (SEE));
- Thrombotic events at other locations;
- Reason for permanent early discontinuation of study drug.

4. STUDY DESIGN AND OVERALL STUDY PLAN

4.1. Study Design

This is a multinational, prospective, randomized, open-label, blind-evaluator (PROBE), non-inferiority study comparing edoxaban with dalteparin for prevention of the combined outcome of recurrent VTE or major bleeding in patients with VTE associated with cancer. Adult subjects with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin; cancer should be active or diagnosed within the previous 2 years), and who present with confirmed acute symptomatic or unsuspected lower extremity proximal DVT, confirmed symptomatic PE, or unsuspected PE in a segmental or larger pulmonary artery for whom long-term treatment (at least 6 months) with LMWH is indicated are eligible to participate in this study.

After a subject's eligibility is confirmed, the subject will be stratified by 1) bleeding risk, and 2) the need for dose adjustment:

1. Bleeding risk (assessed at time of randomization)
    - surgery within 2 weeks prior to randomization
    - use of antiplatelet agents (eg, aspirin ≤ 100 mg/day) that will continue during the study
    - brain tumor or brain metastases present at the time of randomization
    - metastatic disease present at the time of randomization
    - regionally advanced cancer present at the time of randomization
    - gastrointestinal cancer at randomization or diagnosed within a 6-month period prior to randomization
    - urothelial cancer at randomization or diagnosed within a 6-month period prior to randomization
    - Avastin (bevacizumab) use at randomization or given within the 6-week period prior to randomization
2. The need for dose adjustment:
    - body weight ≤ 60 kg, or
    - creatinine clearance (CrCL) between 30 and 50 mL/min inclusive
    - concomitant use of P-gp inhibitors

After stratification, subjects will be randomly assigned via interactive voice/web response system (IXRS) in a 1:1 ratio to one of the two treatment groups: LMWH/edoxaban and delteparin.

After randomization, subjects will be assessed at Month 1, Month 3, and then quarterly thereafter for up to 12 months until they complete the study.

The intention is to treat patients for 12 months with the allocated study treatment. Once 1000 subjects are randomized in the study, a global end-of-treatment (EOT) date will be established that ensures a minimum of 6 months of study treatment and follow-up for the final subject(s) randomized. All subjects will complete or permanently discontinue study treatment on or before the EOT date. Subjects requiring additional anti-coagulation therapy who complete their treatment and full 12-month post randomization follow-up or whose treatment is truncated due to the global EOT date will be managed according to local practice.

Approximately 140 study sites in North America, Europe, and Australia/New Zealand are planned to enroll subjects in this study.

4.2. Overall Study Plan

Regardless of the total duration of study drug treatment actually received, efficacy and safety data will be collected on all subjects, including those who temporarily interrupt or permanently discontinue study drug, during the entire 12-month study period following randomization. For all subjects, contacts (visits or phone calls) are scheduled at regular time points (Protocol Appendix 17.7, Schedule of Events). During these contacts, the treatment and clinical course of the subject will be evaluated. Subjects with suspected efficacy or safety endpoints will undergo confirmatory testing. All subjects, including those who temporarily interrupt or permanently discontinue study drug, will be followed up until Month 12, or until the global EOT date, whichever comes first.

4.3. Treatments

Subjects will be randomized to one of two treatment groups:

- **LMWH/Edoxaban group**: Therapeutic doses of LMWH (SC) will be administered for at least 5 days; this 5-day period may include the pre-randomization LMWH (if applicable). The choice of this parenteral LMWH is up to the treating physician. Thereafter, edoxaban will be started orally at 60 mg QD (2 × 30 mg tablets; 30 mg QD for subjects requiring dose adjustment) for the remainder of the treatment period.
- **Dalteparin group**: After randomization, dalteparin will be administered at a dose of 200 IU/kg SC (maximum daily dose 18,000 IU) for 30 days. The 30 day period may include the pre-randomization anticoagulant treatment if dalteparin

was used in therapeutic doses. Thereafter (approximately Day 31 forward), dalteparin will be administered at a dose of 150 IU/kg SC (~ 75% - 83% of the initial dose) for the remainder of the treatment period.

The edoxaban daily dose should be decreased to 30 mg QD for:

- body weight ≤ 60 kg; or
- creatinine clearance [CrCL] between 30 and 50 mL/min inclusive;
- concomitant use of P-gp inhibitors (eg, hormonal agents: tamoxifen, enzalutamide, abiraterone).

Dose reduction of edoxaban to 30 mg QD is intended only during concomitant use of P-gp inhibitors. When use of these inhibitors is discontinued/intermittent (eg, between chemotherapy cycles) full 60 mg edoxaban dose should be used.

After randomization, if the subject's CrCL becomes ≤ 50 mL/min and ≥ 30 mL/min and the decrease in CrCL is > 20% from the subject's baseline CrCL value, repeat the measurement preferably within 1 week. If the repeat measurement confirms this decrease, the edoxaban dosage regimen will be reduced permanently, even if the subject subsequently experiences improved CrCL to > 50 mL/min at a later measurement.

After randomization, if the subject's body weight drops to ≤ 60 kg (confirmed by repeat measurement at least 1 week apart) and the body weight change is > 10% of the subject's baseline body weight, the edoxaban dosage regimen will be reduced permanently, even if the subject subsequently re-gains weight to > 60 kg.

4.4. Blinding

This study has an open-label, blinded-evaluator design. The subjects, Investigators, Sponsor, Contract Research Organization (CRO), and Academic Research Organization (ARO) staff involved in the treatment or clinical evaluation of the subjects will be aware of the treatments received.

An independent Clinical Events Committee (CEC) will adjudicate and categorize the presenting index diagnosis, VTE outcomes, cardiovascular events, bleeding events, selected hepatic events, and death. Adjudicators will be blinded as to subject treatment allocation.

There will be an independent Data Monitoring Committee (DMC) to periodically review and examine the safety and efficacy data (mortality and events, bleeding events, serious adverse events [SAEs], systemic embolic event [SEE]).

The specifications for generation of the randomization schedule will be prepared by the CRO in charge of the IXRS. For this study, the randomization schedule refers to a list that includes the randomization number, randomization block number, and treatment.

4.5. Determination of Sample Size

Assuming a hazard ratio of 1, a total of 191 overall primary events are projected to accrue in the mITT analysis set which will ensure at least 80% power for the primary analysis at a non-inferiority margin for the hazard ratio of 1.5 and a Type I error of 0.05 (two-sided).

Assuming a primary combined outcome rate (recurrent VTE or major bleed) of 20.0%, a total of 1000 subjects are expected to be randomized to study treatment in order to accrue 191 overall primary events in the mITT analysis set.

5. EFFICACY AND SAFETY ENDPOINTS

5.1. Primary Outcome Endpoint

The primary outcome endpoint is the composite of recurrent VTE, or major bleeding.

Recurrent VTE is either:

- symptomatic confirmed (new) DVT or (new) PE;
- unsuspected (new) proximal DVT, which is a DVT coincidentally detected during other investigations (eg, abdominal or pelvic CT for cancer staging). This DVT will only be included as an outcome if it concerns a (new) clot located in the popliteal or more proximal leg veins. A thrombus detected in the IVC or iliac veins on an abdominal or pelvic CT does not require additional confirmation. A thrombus detected in the common femoral vein or more distal veins can only be confirmed if CUS (or venography) diagnostic criteria are also met.
- unsuspected (new) PE, which is an embolism coincidentally detected during other investigations (eg, CT for cancer staging), that involves segmental or more proximal pulmonary arteries.
- fatal PE (including unexplained death for which PE cannot be ruled out).

Major bleeding is defined as overt bleeding and:

- associated with a decrease in hemoglobin of $\geq$ 2 g/dL, or
- leading to a transfusion of $\geq$ 2 units of packed red blood cells or whole blood, or
- occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- contributing to death.

All suspected recurrent VTE and bleeding events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

5.2. Secondary Efficacy Endpoint

The secondary endpoints include:

- Recurrent VTE
- Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE-related death;

- Recurrent deep vein thrombosis (DVT);
- Recurrent pulmonary embolism (PE);

All investigator reported VTE events, deaths, and bleeding events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

5.3. Safety Endpoints

The primary safety endpoint is major bleeding, and the secondary safety endpoints include the following:

- Major + clinically relevant non-major bleeding;
- Clinically relevant non-major bleeding;
- All bleeding;
- Mortality from all causes.

CEC adjudication results will form the basis for the final analysis. Healthcare resource utilization for potential recurrent VTE and bleed events will also be analyzed.

5.4. Exploratory Safety Endpoint

Exploratory endpoints include:

- CV events (MI, stroke, SEE);
- Thrombotic events at other locations;
- Reason for permanent early discontinuation of study drug.

All investigator reported CV events and other thrombotic events will be adjudicated by the CEC. Adjudicated results will be the basis for the final analyses.

5.5. Drug Concentration, Pharmacodynamic, and Pharmacogenomic Measurements

Not applicable.

6. STATISTICAL METHODS

The data analysis will be performed by Quintiles under the guidance of the sponsor study biostatisticians. SAS version 8.2[1,2,3] or newer will be used in the statistical analysis.

All data will be organized and analyzed according to the scheduled times as outlined in the protocol and by visit as denoted on the Electronic Case Report Form (eCRF).

The clinical database is the source for data used in analyses. The primary data source contains all data (including local laboratory data) reported in the Electronic Data Capture (eDC) database. Other sources of data used in analyses are:

- Event adjudication data from CEC
- Randomization data collected from IXRS including the stratification information.
- Post randomization dose adjustment information from IXRS.

All investigator reported primary, secondary and exploratory endpoint events are captured on the eCRF . All endpoint events reported on the event forms will be adjudicated in a blinded manner by the CEC. The CEC adjudicator's results will be entered into the adjudication database separate from eDC database. The final analyses will be performed based on the CEC's adjudicated outcomes. Investigator reported events will also be summarized.

6.1. General Procedures and Data Presentation

Raw data will be presented with the exact precision (decimal points) with which it was collected. The number of decimal places to display for calculated data will be determined by the scale of the measurement. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when all calculated values are within the interval (10, 100), with 10 being inclusive; 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.

For continuous variables, statistical summaries will include means, medians, standard deviations, maximums, and minimums. Means and medians will be displayed to one more decimal places than the raw or calculated data; standard deviations and other dispersion statistics will have two more decimal places; and minimums and maximums will be displayed to the same number of decimal places as the raw or calculated data.

For categorical variables, statistical summaries will include counts and percentages. Percentages will be reported with exactly one decimal place. In general, percentages are based on the total number of subjects on whom information is available within the analysis set of interest and in that treatment group. For AEs and incidence analyses, percentages are based on the total number of subjects in the analysis set of interest and in that treatment group.

Kaplan-Meier survival curves will be presented for all time to event analyses.

All tests and CIs are 2-sided unless specified otherwise.

All p-values will be displayed with four decimal places.

When the number of events in at least one of the treatment groups is <3, hazard ratios, CIs and p-values will not be presented.

All by visit summaries and analyses will use scheduled nominal visit; if two or more visits have same nominal visit, the first one will be used.

6.2. Adjustments for Covariates

For the primary outcome variable, the time to first event will be analyzed using the Cox proportional hazards model with model terms for treatment group and the following randomization stratification factors:

- Bleeding Risk (Yes; No)
- Need for dose adjustment (Yes; No)

Secondary efficacy and key safety endpoints will be analyzed using the similar Cox proportional hazards model with model terms for treatment group and the same covariates.

6.3. Handling of Dropouts or Missing Data

All analyses will be performed on observed data only and no missing data will be imputed unless otherwise described in the analysis sections. Right censoring will apply for all time to event analyses.

6.3.1. Partial and Estimated Dates

Partial and estimated dates are allowed for some of the date fields as collected on the eCRF. Partial dates will be imputed differently depending on whether the date is, by nature, a baseline date (e.g., the diagnosis date of a medical history) or a post-baseline date (e.g., the onset date of an AE). Estimated dates will be used as collected. In general, a conservative imputation rule will be implemented for all partial dates that will either include more events or result in events being considered part of the On-Treatment Period (i.e., while on study drug or within three days of last dose of study drug).

6.4. Interim Analyses

No formal interim analysis is planned; however, risk-benefit will be evaluated by the DMC and the DMC chairman will alert the chairman of the Joint Steering Committee (JSC) in the event of any clinically concerning safety issues. Access to the DMC tabular risk benefit data will be restricted to DMC members. The procedures of the DMC are described in its charter.

6.5. Data Monitoring Committee (DMC)

An independent DMC will monitor safety during the study and give recommendations to the JSC. This committee will be unblinded to subjects' treatment groups. The primary role for the DMC will be to examine the unblinded safety and efficacy data (VTE events, bleeding events, deaths, MIs, stroke, SEE, thrombotic events at other locations, liver enzyme and bilirubin abnormalities, SAEs) in an ongoing manner and alert the Chairman of the JSC in the event of any clinically concerning safety issues. See the submitted DMC charter for details.

6.6. Clinical Events Committee (CEC)

A CEC will objectively (blinded) adjudicate and categorize the presenting index diagnosis, protocol specified VTE events, bleeding events, deaths, CV events (MI, stroke, SEE), thrombotic events at other locations, selected hepatic dysfunction / liver enzyme elevation. Due to logistical constraints, adjudication of index events will be performed after randomization; hence, these adjudicated index events will not be used to qualify the subject for study, but rather to subsequently define the efficacy analyses sets. Final adjudicated results from the CEC assessments will be recorded in the adjudication database separate from eDC database for final analysis. See the submitted CEC charter for details.

6.7. Data Pooling

No Data pooling is planned for this study.

Summary statistics for key efficacy and safety variables will be provided by region/country.

Region	**Countries**
North America	USA, Canada
Central Europe	Czech Republic, Hungary
South Europe	France, Italy, Spain
Western Europe	Austria, Belgium, Germany, The Netherlands
Australia-New Zealand	Australia, New Zealand

6.8. Multiple Comparisons/Multiplicity

The following test plan will be followed in the efficacy and safety analyses:

Step 1: Test the primary outcome endpoint (overall recurrent VTE or major bleeding) based on the Modified Intent-to-Treat (mITT) Analysis Set for non-inferiority at α=0.05.

Step 2: If non-inferiority is achieved in step 1, then test the primary outcome endpoint (overall recurrent VTE or major bleeding) based on the mITT Analysis Set for superiority at α=0.05.

Step 3: Test the primary safety endpoint (on-treatment major bleeding) based on the Safety Analysis Set for superiority at α=0.05.

7. STATISTICAL ANALYSIS

7.1. Analysis Sets

Randomized Analysis Set: All subjects randomized to treatment.

Modified Intent-to-Treat (mITT) Analysis Set: All randomized subjects who receive at least one dose of post-randomization study drug.

Per Protocol (PP) Analysis Set: All randomized subjects who receive at least one dose of the full study drug regimen[1], who have not experienced treatment misallocation, and for whom the index Deep Vein Thrombosis (DVT) or pulmonary embolism (PE) event at baseline was confirmed by the CEC, and who had at least one active cancer or history of cancer at randomization. Treatment misallocation is defined as a patient taking incorrect treatment during the entire study period.

Safety Analysis Set: All randomized subjects who receive at least one dose of study drug.

Frequency for each analysis set will be summarized by treatment group for all subjects randomized.

7.2. Disposition of Subjects

Enrollment summary will be presented by region, country and treatment group for all subjects randomized.

Disposition of subjects will be summarized for each analysis set by treatment group for the Safety/mITT Analysis Set and the Per Protocol (PP) Analysis Set. This summary includes the total number of subjects completing the study follow-up per protocol**,** completing treatment (all subjects who permanently stop study treatment at a protocol defined stopping point), discontinuing from treatment, and discontinuing from the study follow-up. Reasons for discontinuation from treatment and discontinuation from the study follow-up will be provided. Number of subjects survived in study (<3, ≥3 months) will be summarized. A comparison by the treatment group will also be performed for total number of subjects completing the study follow-up and for those discontinuing the study follow-up.

A summary of study drug discontinuation/interruptions will include, but not be limited to, the following: number and percent of subjects permanently discontinuing study drug and reason, number and percent of subjects with at least one interruption and reason, and number and percent of occurrences of study drug interruptions (1, ≥2 occurrences) for the Safety/mITT Analysis Set and the Per Protocol (PP) Analysis Set.

Overall study period duration will be summarized for the Safety/mITT Analysis Set and the Per Protocol (PP) Analysis Set. Time to premature discontinuation from study by

[1] This means at least one dose of post-randomization edoxaban for subjects assigned to the edoxaban group and at least one dose of post randomization dalteparin for subjects assigned to the dalteparin group

treatment group will be displayed graphically for the Safety/mITT Analysis Set and the Per Protocol (PP) Analysis Set.

Listings will be provided for reasons for study discontinuation and study drug discontinuation separately.

7.3. Protocol Deviations

A descriptive summary and listing of all subjects with major protocol deviations will be provided for the mITT Analysis Set. A descriptive summary of all subjects with major protocol deviations will also be provided for the Per Protocol (PP) Analysis Set. Prior to database lock, review will occur to finalize the list of subjects who meet the criteria for major protocol deviations.

Major protocol deviations are:

- Unconfirmed active cancer, or unconfirmed cancer diagnosed within two years prior to randomization
- Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of DVT and/or PE;
- More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, unfractionated heparin, and fondaparinux per local labeling), oral direct anticoagulants or VKA prior to randomization to treat the current (index) episode;
- Treatment with therapeutic doses of an anticoagulant other than that used for pre-treatment of the current (index) VTE episode prior to randomization;
- Treatment misallocation;
- Concomitant use of disallowed medications (e.g., concomitant anticoagulation therapy) that impact the evaluation of primary outcomes for efficacy and safety;
- CrCL < 30 mL/min or Platelets < 50,000 cc^3 at the time of randomization.
- Unconfirmed index events with Thrombosis in incorrect anatomic location.

Any site for which subject data authenticity is suspect and cannot be confirmed will be identified at a data review meeting and subsequently excluded from all efficacy and safety analyses. Any such decisions will be finalized and recorded prior to database lock. A listing will also be provided to summarize subjects with major protocol deviations.

7.4. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and by Dose Adjustment Status at Randomization for the Safety/mITT Analysis Set and the Per Protocol (PP) Analysis Set. All categorical parameters will be summarized by frequency and percentage based on the number of subjects with available data for that parameter. Variables such as age, body weight, BMI, and CrCL will also be summarized by

descriptive statistics including means, medians, standard deviations, maximums, and minimums.

The following categorical baseline characteristics derived from IXRS will be presented:

- Dose Adjustment at Randomization (yes, no);
- Bleeding risk (yes, no), and number of bleeding risk (0, 1, 2, 3, ≥4). Bleeding risk factors at randomization including:
  - Surgery within 2 weeks prior to randomization
  - Antiplatelet use
  - Brain tumor or brain metastases
  - Metastatic disease
  - Regionally advanced cancer
  - Gastrointestinal cancer at randomization or diagnosed within a 6-month period prior to randomization
  - Urothelial cancer at randomization or diagnosed within a 6-month period prior to randomization
  - Avastin (bevacizumab) use at randomization or given within the 6-week period prior to randomization
- Combination of Dose Adjustment (yes, no) and Bleeding Risk (yes, no);
- Body Weight (≤60.0 kg, >60.0 kg; ≤60.0 kg, 60<-90 kg, >90 kg);
- Creatinine clearance (≥30-≤50 mL/min, >50 mL/min);
- Platelet (50,000-100,000/mL, >100,000/mL);
- P-gp use at randomization (yes, no).

Other categorical baseline characteristics collected from eCRF will include:

- Age (<65, ≥65-<75, ≥75 years);
- Gender
- Race
- Ethnicity (Hispanic/Latino vs Not) for USA subjects only
- Body Weight (≤60.0 kg, >60.0 kg; ≤60.0 kg, 60<-90 kg, >90 kg);
- Body Mass Index;
- Creatinine clearance (<30 mL/min, ≥30-≤50 mL/min, >50 mL/min);
- Presenting diagnosis of DVT or PE
- ECOG performance status
- Past cancer and medical history
- Region/country

The following cancer diagnosis and presenting diagnosis at randomization, confirmed by adjudication, will be presented:

- Type of cancer (Solid Tumor, Haematological Malignancy);
- Active cancer (yes, no);
- Distant metastasis (yes, no);
- Receiving cancer treatment (yes, no);

- Recurrent cancer (yes, no);
- Cancer cured (yes, no);
- Symptomatic DVT, Unsuspected DVT, Symptomatic PE, Unsuspected PE;
- Anatomical extent of qualifying event.

7.5. Measurements of Treatment Compliance

Study drug dosing compliance will be summarized for the Safety/mITT Analysis Sets and the Per Protocol (PP) Analysis Set and will be presented by the three categories: <80%, ≥80% and ≤ 120%, as well as >120% of doses taken.

Edoxaban compliance over the whole treatment period will be calculated as

*(total number of edoxaban tablets taken)/ (total number of edoxaban tablets should be taken)*100*

Total number of edoxaban tablets taken will be calculated as:

∑(amount of dispensed at previous visit – amount of returned at current visit)

Total number of edoxaban tablets that should be taken will be calculated as:

*∑tablets * (days between two visits – planned interruption days)*

For 60 mg dose, 2 tablets are to be taken; 1 tablet to be taken for 30 mg dose.

Treatment compliance for dalteparin will be calculated using the same method but will be accounting for number of dalteparin syringes instead of number of edoxaban tablets.

7.6. Extent of Exposure to Study Drug

Subject exposure will be summarized for the Safety/mITT Analysis Sets and the Per Protocol (PP) Analysis Set and will be presented by total time on study drug at <3 months (<90 days), 3-≤6 months (90-≤180 days) , 6-≤9 months (180-≤270 days), 9<-≤12 months (270<-≤365 days), and >12 months (>365 days) after the first study drug dose. Descriptive statistics, including mean, median, standard deviation, maximum, and minimum, will also be provided for total time on study drug, duration of exposure.

Total time on study drug (exposed to study drug) is defined as the total number of days the subject took study drug, with interruptions not included in the interval of time. For each subject, the total time on study drug may actually be a few days less than the total time in all On-Treatment Periods as it does not include the three days after last dose of study medication.

Total treatment period is defined as the total number of days the subject took study drug, with interruptions included in the interval of time (date of last study dose – date of first study dose +1).

Number of subjects exposed to anti-coagulation therapy prior to randomization will be summarized for the Safety/mITT Analysis Set and the Per Protocol (PP) Analysis Set by

treatment groups as: [LMW] heparin or other anti-coagulation use within the 5 days prior to randomization: None, have been used for ≤ 5 days, and have been used for > 5 days.

7.6.1. Targeted Cancer Therapy

Targeted cancer therapy received on or after initial dose of study drug will be summarized by treatment group for the Overall Study Period and the Safety/mITT Analysis Set and the Per Protocol (PP) Analysis Set.

7.6.2. Concomitant Medications

Targeted and non-targeted concomitant medications taken on or after initial dose of study drug will be summarized separately by treatment group for the Overall Study Period. Medications will be coded using the World Health Organization (WHO) drug dictionary 01June2010 Version or later. Safety/mITT Analysis Set and the Per Protocol (PP) Analysis Set will be used for this analysis.

7.6.3. Non-Drug Therapies

Non-drug therapies performed on or after the initial dose of study drug will be summarized by treatment group for the Overall Study Period. Safety/mITT Analysis Set and the Per Protocol (PP) Analysis Set will be used for this analysis.

7.7. Analysis of Primary Outcome and Efficacy

The following will be applied to all efficacy analyses where applicable.

The mITT and the Per Protocol Analysis Sets will be used in the analysis of primary outcome and all efficacy endpoints. Analyses for all efficacy endpoints will be based on the randomized treatment even if a subject inadvertently receives the incorrect study drug. Endpoints will be summarized by treatment group unless otherwise stated.

The summary statistics for the primary outcome and efficacy endpoints and their individual components will be provided. These statistics include the number of first events (i.e., the number of subjects with the event). For primary outcome and secondary efficacy endpoints, the hazard ratios of the LMWH/edoxaban versus dalteparin with 95% CIs will be provided using the Cox proportional hazards model with model terms for treatment and the randomization stratification factors (bleeding risk, and need for dose adjustment) as covariates. Kaplan-Meier plots[4] of time to events for the endpoint will also be provided by treatment group. CEC adjudication results will be the basis for the primary analysis.

The reference date for efficacy analysis during Overall Study Period will be the randomization date. The reference date analysis during On-Treatment Period will be the first dose date.

Incidence rates of subjects with only 1 event, only 2 events, and >= 3 events will be analyzed for each of the key efficacy endpoints.

Sensitivity analyses will be performed for the all primary outcome and efficacy endpoints based on the Per Protocol Analysis Set.

7.7.1. Adjudicated Efficacy Endpoint Derivations

The detailed definition for each endpoint event is described in the submitted CEC Charter.

7.7.2. Analyses of Primary Outcome and Efficacy Endpoints

7.7.2.1. Analyses of the Primary Outcome Endpoint

7.7.2.1.1. Primary Analysis of the Primary Outcome Endpoint

The primary analysis will compare treatment efficacy for the occurrence of adjudicated composite primary outcome endpoint (recurrent VTE [symptomatic recurrent DVT, unsuspected proximal DVT, non-fatal symptomatic recurrent PE, unsuspected PE, fatal-PE] or major bleed) using the Overall Study Period for all subjects in the mITT Analysis Set. The events that will be counted in this analysis are those events occur from the date of randomization through the end of the 12-month (Day 365) study period, the last available date that the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global EOT, regardless of whether the subject was taking study drug, whichever comes first.

For subjects who do not experience an event, the time to first event will be censored at Day 365, or the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global EOT, whichever comes first. Subjects lost to follow-up, subjects who died because of reasons other than DVT/PE, or subjects who withdrew informed consent before the end of the 12-month treatment period and who did not have a primary outcome, will be censored at the last day the subject had a complete assessment for study outcomes.

The primary outcome analysis is designed to demonstrate that the LMWH/edoxaban Group is non-inferior to the dalteparin Group at a non-inferiority margin of 1.5 for hazard ratio, using a significance level of α=0.05. The time to first event will be analyzed using a Cox proportional hazards model including model terms for treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates. If the upper limit of the two-sided 95% CI of the hazard ratio is below 1.5, then non-inferiority to dalteparin Group will be considered established for the LMWH/edoxaban Group.

The impact of selected baseline covariates on the primary outcome will be described by calculating adjusted Hazard Ratios and corresponding 95% CI of the treatment effect.

The components of primary outcome endpoint (recurrent VTE [symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, unsuspected PE, fatal-PE] or major bleed) for each treatment group will be summarized.

A listing of investigator reported endpoints and their adjudicated results will be provided.

A sensitivity analysis will be performed for the primary outcome endpoint based on the Per Protocol Analysis Set.

7.7.2.1.2. Sensitivity Analyses of the Primary Outcome Endpoint

The following sensitivity analyses will be performed for the Primary Outcome Endpoint:

- On-Treatment events based on the mITT and PP Analysis Set will be analyzed using the counting process approach of the Cox proportional hazards regression model including treatment group, and the stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates. An On-Treatment event is defined as the event occurring during the time period the subject is taking study drug up to 3 days after their last dose for that time period. Only events occurring prior to or on Day 365 will be included into this analysis. Subjects who do not experience an On-Treatment event will be censored at Day 365, or the time study drug is permanently discontinued plus 3 days or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global EOT, whichever comes first.
- Events occurring during the first 6 months (180 days) based on the mITT Analysis Set and the Per Protocol Analysis Set will be analyzed using the same statistical model as the analysis of primary outcome during the Overall Study Period. The time to event is defined as the time (days) from the randomization to the first event during the first 6 months (until Day 180) after randomization. Subjects who do not experience an event until Day 180 will be censored at Day 180, or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, whichever comes first.
- On-Treatment events during the first 6 months (180 days) based on the mITT and PP Analysis Set will also be analyzed using the same counting process approach with the Cox proportional hazards regression model including treatment group, and the stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates. Only On-Treatment events occurring during the first 6 months (until Day 180) will be included into this analysis. Subjects who do not experience an On-Treatment event will be censored at Day 180 if they are still on study drug on Day 180, or the time study drug is permanently discontinued plus 3 days if the discontinuation is before Day 180, or on the last day the subject had a complete assessment (in-person visit or by telephone) for study outcomes, or the day of global EOT, whichever comes first.
- The same analyses for primary outcome endpoint based on the mITT Analysis Set and the Per Protocol Analysis Set during Overall Study Period, and the mITT Analysis Set and the Per Protocol Analysis Set during the first 6 months study period, will also be carried out by dose adjustment status at randomization.

7.7.2.1.3. Superiority Analysis of the Primary Outcome Endpoint

If non-inferiority in the primary outcome is established, LMWH/edoxaban will be compared to dalteparin for superiority (α=0.05, two-sided) with regard to the time to an event in the composite clinical outcome of recurrent VTE or major bleed during the 12-month study period. This analysis will be based on the mITT Analysis Set during the Overall Study Period using the same proportional hazard model as for the primary outcome. The same analysis will also be carried out using the same proportional hazard model with counting process for the On-Treatment Period for the mITT. The same analysis will also be carried out for the Per Protocol Analysis Set.

7.7.2.2. Analysis of the Secondary Efficacy Endpoint

Analysis for the secondary efficacy endpoints will be performed using the Overall Study Period for the mITT Analysis Set using Cox proportional hazards model including model terms for treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates. Descriptive summaries will also be provided. Secondary efficacy endpoints include:

- recurrent VTE;
- event-free survival: the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;
- VTE -related death;
- recurrent DVT;
- recurrent PE.

The same event inclusion and censoring method used in primary outcome endpoint will be applied to secondary efficacy endpoints. The LMWH/edoxaban will be compared to dalteparin for superiority (α=0.05, two-sided) with regard to the time to an event in recurrent VTE during the Overall Study Period.

Same sensitivity analyses used in primary outcome analysis will also be applied to secondary efficacy endpoints, which include:

- Events occurring during the first 6 months (180 days) based on the mITT Analysis Set using the Initial 6-Month Study Period.

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.7.2.3. Subgroup Analyses for the Primary Outcome and Secondary Efficacy Endpoints

Subgroup analyses will be performed for the primary outcome and secondary efficacy endpoints using the Overall Study Period approach for the mITT Analysis Set, and the Initial 6-Month Study Period for the mITT Analysis Set. Descriptive summaries will be provided. The percentages will be based on the total number of subjects that make up the subgroup being summarized, regardless if an event occurred**.** Forest plots will be generated for subgroup analyses.

Subgroups will be based on characteristics including, but not limited to, the following:

1. Presenting diagnosis of DVT or PE (Symptomatic vs Unsuspected). Adjudicated results will form the basis for the subgroup analysis. In the instance the CEC is unable to confirm the diagnosis, the investigators' diagnosis will be used).
2. Presenting diagnosis of DVT only, vs PE with or without DVT
3. Age (<65 years vs. ≥65 years, <75 years vs. ≥75 years)
4. Gender (male vs. female)
5. Race (White, Other than white)
6. Weight (<60, 60-90, >90 kg)
7. Prior VTE (yes, no)
8. Dose adjustment at randomization (yes, no)
9. CrCL at randomization (≥30-≤50 mL/min, >50 mL/min)
10. Platelet at randomization (50,000-100,000/mL vs > 100,000/mL)
11. P-gp use at randomization (yes, no)
12. Bleeding Risk at randomization (yes, no), and bleeding risk factors including:
    - Surgery within 2 weeks prior to randomization
    - Antiplatelet use
    - Brain tumor or brain metastases
    - Metastatic disease
    - Regionally advanced cancer
    - Gastrointestinal cancer at randomization or diagnosed within a 6-month period prior to randomization
    - Urothelial cancer at randomization or diagnosed within a 6-month period prior to randomization
    - Avastin (bevacizumab) use at randomization or given within the 6-week period prior to randomization
13. Combination of Dose Adjustment (yes, no) and Bleeding Risk (yes, no)
14. Survival in study (<3 Months, >=3 Months)
15. Cancer diagnosis at randomization confirmed by adjudication:
    - Type of cancer (Solid Tumor, Haematological Malignancy)
    - Active cancer (yes, no)
    - Distant metastasis (yes, no)
    - Receiving cancer treatment (yes, no)
    - Recurrent cancer (yes, no)
    - Cancer cured (yes, no)

16. Baseline ECOG Performance Status
17. Initial heparin treatment duration on or after randomization (for example, <5 days, 5-7 days, 8-10 days, >10 days; ≤median, >median; ≤25th percentile, >25th-50th percentile, >50th-75th percentile, >75th percentile). The categorical groups will be determined based on subjects in each category prior to database lock
18. Heparin use prior to randomization (yes, no)
19. Anatomical extent of qualifying event.

The incidence of VTE based on each subgroup will be estimated and a 95% CI for the LMWH /edoxaban: dalteparin hazard ratio will be constructed.

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.7.2.4. Exploratory Efficacy Analyses

The impact of baseline covariates on the primary outcome will also be described by calculating adjusted hazard ratios and corresponding 95% CIs for the treatment effect.

The investigator reported events for primary and secondary endpoints will be summarized using Overall Study Period approach for the mITT analysis set.

Summary of agreement between investigator and adjudicator for investigator reported, confirmed and CEC confirmed primary and secondary efficacy endpoints will be provided by treatment group for the mITT Analysis Set.

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.8. Analysis of Safety

The following procedures will be applied to all safety endpoints unless otherwise stated in the individual sections.

Safety analyses will be summarized for all subjects included in the Safety Analysis Set by treatment group. Analyses for all safety endpoints will be based on randomized treatment, unless a subject inadvertently receives the incorrect study drug during the entire study, in which case, the subject will be grouped according to the treatment actually received. The time periods used for analyses are described for each safety parameter. Adjudicated safety events along with select key investigator reported safety events will be analyzed. All remaining safety results will be summarized descriptively.

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.8.1. Safety Event Derivations

Detailed definitions for bleeding categories are described in the submitted CEC Charter.

7.8.1.1. Analysis of the Primary and Secondary Safety Endpoints

The primary safety endpoint is major bleeding events that occur during On-Treatment Period (on study drug or up to 3 days after the last dose for that time period.)

The time from date of initial study dose to first major bleeding will be compared between treatment groups for superiority (α=0.05 two-sided) for subjects in the Safety Analysis Set, using a Cox's proportional hazard regression model with counting process using the model terms for treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates.

For subjects did not experience any event, they will be censored 3 days after the day of permanent study medication discontinuation, the last day the subject had a complete assessment for study outcomes, or the day of global EOT, whichever comes first.

Subjects who experience multiple major bleeding events will be summarized by treatment groups.

Incidence and Hazard Ratio (with 95% CI) for the following secondary safety outcomes will be calculated based on the Safety Analysis Set and On-Treatment-approach using the Cox proportional hazards regression model with counting process approach with the model terms for treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates:

- Clinically relevant non-major bleeding
- Major + clinically relevant non-major bleeding
- All bleeding

Both primary and secondary safety endpoints for bleedings will be analyzed using the following approaches for the Safety Analysis Set:

- Events during Overall Study Period analyzing by Cox proportional hazard regression model with the treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates.
- Events during the first 6 months On-Treatment Period (180 days) analyzing by Cox proportional hazards regression model with counting process including treatment group, and the stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates.

Adjudicated bleeding events will also be summarized by category, location, characteristics, and circumstance as recorded in the CRF for major bleeding, clinically relevant non-major bleeds, and major plus clinically relevant non-major bleeds. All investigators reported bleeds will be summarized separately from adjudicated bleeds.

Adjudicated death events occurred during Overall Study Period described above will also be analyzed using a Cox's proportional hazard regression model with the treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates for subjects in the Safety Analysis Set. Subjects will be censored after the last day the subject had complete assessment (in-person visit or by telephone) for study outcomes, or the day of global EOT, whichever comes first.

A listing of investigator reported endpoints and their adjudicated results will be provided. Adjudicated events for subjects who did not expose to study drug Edoxaban will also be listed.

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.8.1.2. Healthcare Resources Utilization

The incidence of hospital admission related to recurrent VTE or bleeding events will be summarized by treatment group for the Safety Analysis Set using the Overall Study Period. Total number of days in hospital, intensive care unit, step-down ward and general hospital ward will be descriptively summarized.

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.8.1.3. Exploratory Safety Endpoints

Incidence and Hazard Ratio (with 95% CI) will be calculated based on the Safety Analysis Set and On-Treatment-approach using the Cox proportional hazards regression model with counting process and with the model terms for treatment and the randomization stratification factors (bleeding risk and need for dose adjustment as binary variables) as covariates.

The exploratory safety endpoints include:

- CV events (MI, stroke, SEE)
- Thrombotic events at other locations.

Exploratory safety endpoints occurred during the Overall Study Period described above will also be analyzed for subjects in the Safety Analysis Set.

The investigator reported endpoints will be summarized separately for the On-Treatment Period and Overall Study Period.

Summary of agreement between investigator and adjudicator for investigator reported, confirmed and CEC confirmed safety endpoints will be provided by treatment group for the Safety Analysis Set.

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.8.1.4. Subgroup Analyses for the Primary and Secondary Safety Endpoint

Subgroup analyses will be performed for the adjudicated major bleeding, major or CRNM bleeding using the Safety Analysis Set for the On-Treatment Period, the Overall Study Period, and the Initial 6-Month On-Treatment Period. Descriptive summaries will be provided. Percentages will be based on the total number of subjects that make up the subgroup being summarized, regardless if an event occurred**.** Forest plots will be generated for subgroup analyses. No inferential analysis will be conducted unless specified otherwise. Subgroups to be used for safety analysis will be the same as those for efficacy analysis.

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.8.2. Liver Enzyme and Bilirubin Abnormalities

Liver enzyme and bilirubin abnormalities will be summarized by treatment group using the On-Treatment Period and the Overall Study Period for the Safety Analysis Set. These summaries will be for based on the adjudicated data, the investigator reported data, and the local laboratory data. In addition, subject listings will be presented for those subjects with reported abnormalities whose cases are sent to adjudicators.

Based on the adjudication information completed by the adjudicators, the nature, clinical severity, and causality of an event and whether Hy's law was satisfied will be presented. The number of subjects adjudicated as having hepatocellular injury will be summarized.

Furthermore, regardless of the investigator reports, all local laboratory results will be evaluated by treatment group for the incidence of elevated liver enzymes for the Safety Analysis set during the On-Treatment Period and the Overall Study Period. The number and percentage of subjects with elevation of liver enzymes according to various multiples of Upper Limit of Normal (ULN) (Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) ≥3xULN, ≥5xULN, ≥8xULN, ≥10xULN, ≥20xULN; total bilirubin ≥1.5xULN, ≥2xULN, ≥3xULN, ≥5xULN) will be summarized by treatment group. A combination of ALT and/or AST ≥ 3xULN accompanied by concurrent (within 37 days after the maximum AST/ALT) total bilirubin ≥2xULN will be summarized. Incidence of Alkaline Phosphatase (ALP) will be summarized using cutoffs of ≥1.5xULN, ≥2xULN, ≥3xULN, as well as confirmed elevation using these same boundaries. Additional combinations of (ALT and/or AST ≥ 3xULN accompanied by concurrent total bilirubin ≥ 2xULN and ALP ≥ 2xULN) and (ALT and/or AST ≥ 3xULN accompanied by concurrent total bilirubin ≥ 2xULN and concurrent ALP < 2x ULN) will be presented and analyzed. For laboratory data, the assessments performed prior to or on the first dose date will be excluded.

A listing with clinically significant abnormal values for these hepatic laboratory results will be provided. In addition, a listing for these hepatic laboratory results and cause of liver enzyme elevations for subjects who had at least one liver enzyme elevation will also be provided.

Scatter plots of Peak AST/ALT vs. Peak Total Bilirubin will be displayed for the Overall Study Period. A separated scatter plot of Peak AST/ALT vs. Peak Total Bilirubin after first study drug dose (i.e. excluding post-randomization LMWH exposures).

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.8.3. Adverse Events

Two sets of AE summaries will be presented:

1. All AEs excluding investigator confirmed VTE, bleeding, MI, Stroke, SEE, and thrombotic events.
2. For all investigator confirmed VTE, bleeding, MI, Stroke, SEE, and thrombotic events.

All adverse event (AE) summaries will be presented by System Organ Class (SOC) and by Preferred Term (PT) within each SOC as classified by the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary[5] Version 12.0 or newer.

The primary Treatment-emergent Adverse Event (TEAE) analyses will be presented using the On-Treatment Period and the Overall Study Period for the Safety Analysis Set. TEAEs are defined as an event that emerge during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state.

An overall incidence summary of AEs with corresponding 95% CIs for incidence rates will be provided, which includes the following:

- Number and percent of subjects with at least one Treatment-emergent Serious Adverse Event (TESAE).
- Number and percent of subjects with at least one TEAE.
- Number and percent of subjects with at least one drug-related TEAE.
- Number and percent of subjects with at least one TEAE with fatal outcome.
- Number and percent of subjects with at least one TEAE that caused study drug permanent discontinuation.

This summary will also be presented for all AEs including investigator confirmed VTE, bleeding, MI, Stroke, SEE, and thrombotic events.

Incidence rates by SOC and PT will be presented by treatment group for the following:

- TEAEs/ TESAEs
- Drug-related TEAEs
- TEAEs by maximum severity (only for AEs excluding investigator confirmed events)
- TEAEs with fatal outcome

Incidence rates by PT in descending order of frequency will be presented by treatment group for the following:

- TEAEs that caused study drug permanent discontinuation

All AEs will be presented in a subject listing. Any AEs leading to permanent discontinuation of study drug will also be presented in a subject listing. AEs for subjects who had at least one adjudicated major bleeding event will be presented in listing separately.

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.8.4. Clinical Laboratory Evaluations

The clinical laboratory evaluations at each scheduled visit and the change from baseline will be summarized for the Safety Analysis Set by treatment group. Shift from baseline with specific clinically meaningful ranges for select clinical local laboratory evaluations will be summarized by treatment group. This will be summarized at each scheduled visit, last assessment and at the worst assessment. If a laboratory retest occurs within a day, then the later value will be used for summarization.

The number and percentage of subjects with clinically relevant abnormal laboratory values will be calculated for each treatment group for selected laboratory parameters. Percentages for these summaries will be based on the available data, rather than the total number of subjects.

The same analyses will also be carried out for the Per Protocol Analysis Set.

7.8.5. Vital Signs and Physical Exam

Observed values of vital signs including systolic and diastolic blood pressure (mmHg), pulse (bpm), weight (kg) and height (cm) collected at randomization will be summarized. Observed and changed from baseline in weight collected at each scheduled visit will also be summarized.

Clinically significant physical examination findings will be listed by treatment group for each body system.

The same analyses will also be carried out for the Per Protocol Analysis Set.

8. REFERENCES

[1] What's New in SAS® Software for Release 8.2. SAS Institute Inc., Cary, NC, 2001.

[2] SAS/STAT® Software: Changes and Enhancements, Release 8.2. SAS Institute Inc., Cary, NC, 2001.

[3] SAS Institute, Inc. SAS OnlineDoc Version Eight. SAS Institute, Inc, Cary, NC, 1999.

[4] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.

[5] Medical Dictionary for Regulatory Activities (MedDRA), Version 12.0.
The International Federation of Pharmaceutical Manufacturers Association (IFPMA), International Committee on Harmonization, Geneva, Switzerland, 2001.

9. LIST OF APPENDICES

I	Comments from the Regulatory Agencies
II	Schedule of Evaluations
III	Trigger Terms
IV	Selected Table Shells

Summary of Main Changes in Statistical Analysis Plan from

Version 1.0 Dated 29 February 2016 through Version 3.0 Dated 02 October 2017

1. Initial 6-Month On-Treatment Period was defined and added: The time period the subject is taking study drug up to 3 days after their last dose or up to Day 180, whichever comes first.
2. Analysis of Adjudicated Recurrent Venous Thromboembolism (VTE) or Major Bleeding Event, Analysis of Adjudicated Bleeding Events, Subgroup Analysis of Adjudicated Major Bleeding Events, and Subgroup Analysis of Adjudicated Major or Clinically Relevant Non-Major Bleeding Events were added for Initial 6-Month On-Treatment Period.
3. Section 6.1, New sentence was added: When the number of events in at least one of the treatment groups is <3, hazard ratios, CIs and p-values will not be presented.
4. New summary for Demographic and Other Baseline Characteristics were added:

a. number of bleeding risk (0, 1, 2, 3, ≥4);
b. Combination of Dose Adjustment (yes, no) and Bleeding Risk (yes, no);
c. New Body Weight (≤60.0 kg, 60<-90 kg, >90 kg);
d. Platelet (50,000-100,000/mL, >100,000/mL);
e. Creatinine clearance (<30 mL/min, ≥30-≤50 mL/min, >50 mL/min);
f. Type of cancer (Solid Tumor, Haematological Malignancy);
g. Active cancer (yes, no);
h. Distant metastasis (yes, no);
i. Receiving cancer treatment (yes, no);
j. Recurrent cancer (yes, no);
k. Cancer cured (yes, no);
l. Symptomatic DVT, Unsuspected DVT, Symptomatic PE, Unsuspected PE.

5. Section 7.6, Exposure to study drug was revised as: <3 months (<90 days), 3-≤6 months (90-≤180 days) , 6-≤9 months (180-≤270 days), 9<-≤12 months (270<-≤365 days), and >12 months (>365 days).

From

3 months (>=85 days), 6 months (>=175 days) and 12 months (>=353 days).

6. Following subgroup analyses were added:

a. Presenting diagnosis of DVT or PE (Symptomatic vs Unsuspected);
b. Weight (<60, 60-90, >90 kg);
c. Prior VTE (yes, no);
d. CrCL at randomization (≥30-≤50 mL/min, >50 mL/min);
e. Combination of Dose Adjustment (yes, no) and Bleeding Risk (yes, no);
f. Survival in study (<3 Months, >=3 Months);
g. Cancer diagnosis at randomization confirmed by adjudication;

Subgroup analysis, CrCL at randomization: 30-<60, 60-<90, >=90 mL/min, was removed.

7. Per Protocol (PP) Analysis Set was defined: All randomized subjects who receive at least one dose of the full study drug regimen[1], who have not experienced treatment misallocation, and for whom the index Deep Vein Thrombosis (DVT) or pulmonary embolism (PE) event at baseline was confirmed by the CEC. Treatment misallocation is defined as a patient taking incorrect treatment during the entire study period

[1] This means at least one dose of post-randomization edoxaban for subjects assigned to the edoxaban group and at least one dose of post randomization dalteparin for subjects assigned to the dalteparin group