CLINICAL STUDY PROTOCOL

A PHASE 1B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER, SINGLE ASCENDING DOSE STUDY TO ASSESS THE SAFETY, EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF DS-1040B WHEN ADDED TO STANDARD OF CARE ANTICOAGULATION THERAPY IN SUBJECTS WITH ACUTE SUBMASSIVE PULMONARY EMBOLISM

DS1040-B-U107

IND/EudraCT NUMBER: 128380/2015-005211-32

VERSION 1.0, 21 JAN 2016

DAIICHI SANKYO INC

399 THORNALL STREET
EDISON, NJ 08837, USA

INVESTIGATOR AGREEMENT

A PHASE 1B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER, SINGLE ASCENDING DOSE STUDY TO ASSESS THE SAFETY, EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF DS-1040B WHEN ADDED TO STANDARD OF CARE ANTICOAGULATION THERAPY IN SUBJECTS WITH ACUTE SUBMASSIVE PULMONARY EMBOLISM (DS1040-B-U107)

Sponsor Approval:

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

[redacted]	[redacted]
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:	2015-005211-32
IND Number:	128380
Protocol Number:	DS1040-B-U107
Investigational Product:	DS-1040b
Active Ingredient(s)/INN:	DS-1040b
Study Title:	A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Single Ascending Dose Study to Assess the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of DS-1040b when Added to Standard of Care Anticoagulation Therapy in Subjects with Acute Submassive Pulmonary Embolism
Study Phase:	Phase 1b/Proof-of Concept
Indication Under Investigation:	Pulmonary Embolism (PE)
Study Objectives:	Primary Objective: To assess the safety and tolerability of ascending doses of DS-1040b given as a single intravenous (IV) infusion over 12, 24, 48 and 72 hours (h), respectively, when added to standard of care (SOC) anticoagulation therapy compared to placebo by evaluating the rate of adjudicated clinically relevant bleeding (International Society of Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major (CRNM) bleeding). Secondary Objectives: To assess the following efficacy endpoints as evaluation of proof-of-concept: 1. Relative reduction (% reduction) in total thrombus volume from baseline to ≤ 12h from end of DS-1040b infusion, assessed by computed tomography angiography (CTA) in segmental or larger pulmonary arteries; 2. Proportion of subjects who achieve a ≥ 20% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of

	DS-1040b infusion and compared to placebo; 3. Proportion of subjects who achieve a ≥ 50% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion and compared to placebo; 4. Recurrence of adjudicated venous thromboembolism [VTE] (Composite of recurrent PE, new or recurrent deep vein thrombosis (DVT), VTE-related death; as well as the individual components) up to hospital discharge and up to Day 30 Visit after dosing; 5. Death, major cardiovascular events (MACE: defined as a composite of cardiovascular death or non-fatal myocardial infarction, stroke, or systemic embolic events [SEE]), hemodynamic decompensation, treatment escalation (defined as catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter) up to hospital discharge and up to Day 30 Visit after dosing; 6. Overall safety evaluation (serious adverse events [SAEs], treatment-emergent adverse events [TEAEs], clinical laboratory parameters); 7. Pharmacokinetics (PK) of DS-1040b in subjects with PE. 8. Assess the pharmacodynamic (PD) effect of DS-1040b on thrombin-activatable fibrinolysis inhibitor (TAFIa) activity, TAFI antigen and D-dimer fibrinolysis biomarkers, in subjects with PE. <u>Exploratory Objective</u>: Assess the effect of DS-1040b on clot lysis as a biomarker for TAFIa activity in subjects with PE.
Study Design:	This will be a randomized, double-blind, placebo-controlled, multi-center, single ascending dose study in subjects with acute PE characterized as low-risk or intermediate-risk or submassive PE. This study will follow an adaptive design and include up to six sequential, ascending-dose/continuous infusion time

cohorts, organized in three pairs (1-2, 3-4, and 5-6) and up to two dose optimization evaluations planned in between the first and second pair of cohorts.

All subjects participating in this study will receive SOC anticoagulation therapy as per the current treatment guidelines for patients with acute PE, to ensure an effective therapeutic background. Due to the early stage of development and in order to minimize variability, the background anticoagulation regimen for this study will be standardized for all subjects to enoxaparin 1 mg/kg, subcutaneous, every 12 hours followed by edoxaban 60 mg (30 mg for subjects requiring dose adjustment) per oral, once daily through the final evaluation at Day 30. Following the end of the study, Savaysa®/Lixiana® (edoxaban, per oral, once daily) will be made available at no cost to the patients for at least 90 days, at the Investigator's discretion per the current treatment guidelines[1]. At the time of randomization, eligible subjects must initiate or be transitioned to the study-specified enoxaparin regimen. The enoxaparin administration will continue for 5 days (6 days for Cohort 6) to cover the infusion with blinded study drug and an additional 72 hours following the end of the study drug infusion needed to ensure an adequate washout and complete the sample collection for PK/PD and biomarker measurements, before the subjects may be switched to edoxaban. Randomized subjects will receive an IV infusion with study drug (either DS-1040b or placebo) over a period of time ranging from 12h to 72h depending on the cohort. All subjects within a cohort will receive the same dose of study drug administered via IV infusion of the same duration. The assignment to either active drug or placebo will be blinded to the subjects and study site staff who may come in direct contact with the subjects as well as to the Sponsor and Medpace study team. The study may be stopped at any time for safety reasons.

An independent, unblinded, Data Monitoring Committee (DMC) will review key safety parameters for each cohort and provide its endorsement for the continuation of the study and the dose escalation decisions. A blinded Clinical Events Committee (CEC) will be established to adjudicate bleeding events.

Study enrollment will be done in pairs of cohorts, beginning with Cohorts 1 and 2, followed by Cohorts 3

	and 4, then 5 and 6. Within each pair of cohorts, subject enrollment will be staggered for safety. Enrollment in Cohorts 2, 4, and 6 will begin after the first 10 subjects in Cohorts 1, 3, and 5, respectively have successfully completed study drug administration and have reached 72 hours post the end of study drug infusion (when the sample collection for PK/PD measurements ends) without any increase in the primary safety endpoint (clinically relevant bleeding) or other relevant safety concerns emerging, as assessed by the independent, unblinded DMC. In Cohorts 1 and 2 eligible subjects will be randomized in a 2:1 ratio to either DS-1040b or placebo. Beginning with Cohort 3 the randomization ratio will change to 3:1. A dose optimization evaluation is planned after all subjects in Cohorts 1-2 reach 72h post end of infusion, which will include imaging (total thrombus volume reduction from baseline to ≤ 12 hours post end of study drug infusion), pharmacokinetic, and select biomarker data. The optimized dose(s) and dosing regimens will be then used for the subsequent cohorts. If necessary, a second dose optimization evaluation may be carried out after Cohorts 3-4 are completed, to further optimize the dose(s) and dosing regimens for Cohorts 5-6. The dose optimization evaluation(s) will be carried out in an unblinded fashion by a separate, designated team with the appropriate firewalls in place to prevent accidental unblinding of the study team. The study may end after Cohorts 3-4 are completed, should the optimized dose(s) and dosing regimens tested yield a clinically meaningful reduction in thrombus size/volume and have acceptable safety and tolerability.
Study Duration:	Duration of subject participation will be approximately 30 days from study qualification through final follow-up. Duration of subject treatment with the blinded study drug, administered as a continuous IV infusion, will be either 12, 24, 48, or 72 hours, depending on the cohort. The duration of the continuous IV infusion with study drug will be the same for all subjects in the same cohort. This study will end once the last subject in the last cohort has completed the evaluation at the Day 30 Visit.

Study Centers and Location:	Approximately 42 sites in North America and Europe.
Subject Eligibility Criteria:	Inclusion Criteria: 1. Male or female subjects, age 18 to 75 years and body weight between 50 and 120 kg, inclusive; 2. Subjects admitted to hospital with a clinical diagnosis of acute PE categorized as low risk or intermediate-risk or submassive PE and for whom catheter-based therapy is not planned; a. Subjects must have a CTA scan confirming the PE diagnosis and with at least one measurable index lesion in a segmental or larger pulmonary artery prior to randomization; b. Subjects should be in otherwise satisfactory health in the opinion of the Investigator; c. Subjects may have concurrent DVT and have an inferior vena cava (IVC) filter placed prior to randomization; d. Subjects may already be on SOC low molecular weight (Heparin) [LMW (Heparin)] at the time of randomization but for no longer than 36 hours. 3. Able to provide written informed consent. Exclusion Criteria: 1. Subjects with acute PE categorized as high-risk or massive, or who are hemodynamically unstable, evidenced by a heart rate > 120 /min and a systolic blood pressure (SBP) of < 90 mmHg for more than 15 consecutive minutes or a drop in SBP of > 40 mmHg since presentation; 2. Subjects for whom use of a thrombolytic, either systemic or via catheter, is planned; 3. Subjects with PE lesions only in the sub-segmental or smaller arteries, which due to limitations of the imaging method may not be consistently identified and measured; 4. Subjects unable or unwilling to take the study-sourced SOC anticoagulation therapy; 5. Subjects receiving any vitamin K antagonists

(VKAs) prior to randomization or receiving more than 36 hours treatment with LMW(Heparin) in therapeutic doses prior to randomization;

6. Subjects who had prior intracranial hemorrhage, known arteriovenous malformation or aneurysm, or evidence of active bleeding;
7. Subjects with a platelet count < 100,000, international normalized ratio (INR) > 1.7, or an elevated partial thromboplastin time;
8. Subjects who within 48 hours of randomization have used an anti-Factor IIa agent such as dabigatran or an anti-FXa agent such as rivaroxaban, apixaban, or edoxaban;
9. Subjects with history of endocarditis;
10. Subjects with < 6 month history of acute coronary syndrome (ACS) whether or not they have undergone percutaneous coronary intervention (PCI);
11. Subjects who require ongoing dual antiplatelet therapy or treatment with aspirin alone in a dosage of more than 100 mg/per day;
12. 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;
13. Subjects with uncontrolled hypertension at randomization, evidenced by SBP > 180 mm Hg or diastolic blood pressure>120 mmHg, or who require parenteral medication to maintain blood pressure below these limits;
14. Subjects who within 3 months prior to randomization have had intracranial surgery, clinically significant head trauma (in the opinion of the Principal Investigator), a stroke, or have received thrombolytic treatment;
15. Subjects with ECG evidence of 2nd degree or higher atrioventricular (AV) block or with QTcB or QTcF > 450 ms;
16. Subjects who within 21 days prior to randomization have had gastrointestinal or

genitourinary bleeding;

17. Subjects who within 14 days prior to randomization have had major surgery or a lumbar puncture (or epidural steroid injection);
18. Subjects with hemoglobin < 10 g/dL;
19. Subjects with an estimated glomerular filtration rate (using Modification of Diet in Renal Disease equation) < 60 mL/min/1.73 m^2;
20. Subjects with diagnosed active liver disease or with elevation of liver enzymes/bilirubin:
    a. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 2 times upper limit of normal (ULN)
    b. Total bilirubin (TBL) ≥ 1.5 times ULN (except due to confirmed Gilbert's syndrome)
21. Subjects with known history of testing positive for Hepatitis B antigen or Hepatitis C antibody before randomization;
22. Subjects with known history of testing positive for the human immunodeficiency virus (HIV);
23. Subjects with active malignancy (diagnosed within 5 years) except for adequately treated non-melanoma skin cancer or other non-invasive or in-situ neoplasm (eg, cervical cancer in situ);
24. Subjects undergoing chemotherapy or radiation therapy in the 30 days prior to randomization or expected to initiate such therapy during study participation;
25. Subjects with congestive heart failure;
26. Subjects with chronic obstructive pulmonary disease;
27. Female subjects of child bearing potential with a positive pregnancy test or who are lactating, or unwilling to use reliable means of contraception (physical barrier, patient or partner) in conjunction with a spermicidal product, contraceptive (pill, patch, injectable), or intrauterine devices (IUDs) following treatment period and through the Day 30 final follow-up visit;

	28. Subjects currently participating in another investigational study or who have participated in an investigational drug study within 30 days or prior to randomization; 29. Subjects unlikely to comply with the protocol (eg, uncooperative attitude, inability to return for subsequent visits, and/or otherwise considered by the investigator to be unlikely to complete the study); 30. Subjects with any condition (including laboratory abnormalities) that, in the opinion of the Investigator, would potentially place the subject at increased risk of harm through participation in this study.
Dosage Form, Dose and Route of Administration:	DS-1040b Injection 10 mg/10 mL vial will be transferred into IV infusion solution (0.9% Sodium Chloride Injection, USP). The placebo for DS-1040b will be 0.9% Sodium Chloride Injection, USP. The blinded solution containing either DS-1040b or placebo will be administered as a single, continuous IV infusion. The IV infusion will consist of an initial loading dose of 3-6 mg (depending on the cohort) administered as a 0.5 hour infusion followed by a maintenance dose with the balance of the total dose administered over the remaining time for the respective cohort (11.5h for Cohort 1, 23.5h for Cohorts 2 and 3, up to 47.5h for Cohorts 4 and 5, and up to 71.5h for Cohort 6). The DS-1040b total doses for Cohorts 1 and 2 are 20 mg over 12h and 40 mg over 24h, respectively. These doses have been shown in healthy volunteers to be safe and well tolerated and to provide an almost complete inhibition of TAFI activity. Up to two dose optimization evaluations are planned using imaging, PK/PD, and biomarker data from Cohorts 1-2 and 1-4, respectively, to optimize the total dose of DS-1040b and infusion duration for the remaining cohorts. Background anticoagulation therapy per the current SOC will be standardized across all study sites and subjects to enoxaparin 1 mg/kg, subcutaneous, every12h for 5 days (6 days for Cohort 6) followed by edoxaban 60 mg (30 mg for subjects requiring dose adjustment) per oral, once daily

	through the end of study visit, at Day 30. Both enoxaparin and edoxaban will be provided as open label and used in accordance to their approved labels. Following the end of the study, Savaysa®/Lixiana® (edoxaban, per oral, once daily) will be made available at no cost to the patients for at least 90 days, at the investigator's discretion per the current treatment guidelines[1] .
Study Endpoints:	Efficacy Endpoints: 1. Relative reduction (% reduction) in total thrombus volume from baseline to ≤ 12h from end of DS-1040b infusion assessed by CTA) in segmental or larger pulmonary arteries; 2. Proportion of subjects who achieve a ≥ 20% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion; 3. Proportion of subjects who achieve a ≥ 50% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion; 4. Death, hemodynamic decompensation, or treatment escalation up to hospital discharge and up to Day 30 Visit. Treatment escalation is defined as catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter; 5. Recurrence of VTE (composite of recurrent PE, new or recurrent DVT, VTE-related death; as well as the individual components) up to hospital discharge and up to Day 30 Visit; 6. MACE (defined as a composite of cardiovascular death, non-fatal myocardial infarction, stroke, or systemic embolic events) up to hospital discharge and up to Day 30 Visit. Safety Endpoints: 1. Clinically relevant bleeding (ISTH major or CRNM bleeding);

	2. Serious adverse events and TEAEs. PK/PD Endpoints: 1. Plasma concentrations of DS-1040a: a. Area under concentration-versus-time curve, from time 0 to the last quantifiable concentration sampling point (AUC_{last}); b. Area under concentration-versus-time curve, from time 0 extrapolated to infinity (AUC_{0-inf}), if data allows c. maximum (peak) observed plasma concentration (C_{max}); d. time of maximum observed concentration (T_{max}); e. Plasma concentration immediately prior to the end of continuous infusion; f. Elimination half-life ($T_{1/2}$), if data allows g. Total clearance (CL), if data allows 2. Pharmacodynamic endpoints including: a. total TAFIa activity; b. D-dimer; c. TAFI antigen; Exploratory Endpoints: 1. Evaluation of clot lysis as a biomarker for TAFIa activity.
Planned Sample Size:	Approximately 22 subjects will be enrolled per cohort, to yield at least 18 evaluable subjects for Cohorts 1-2 and at least 20 for Cohorts 3 - 6 for a total of 118 evaluable subjects. The randomization ratios of DS-1040b to placebo are 2:1 for Cohorts 1 - 2 and 3:1 for Cohorts 3 - 6. A subject will be deemed evaluable if he/she has valid CTA imaging evaluations at both baseline and at the ≤12h post-end of infusion and has successfully completed administration of the blinded study drug infusion. Randomized subjects who do not complete the blinded study drug administration (ie, subjects who stop the IV infusion early due to AEs) will still be followed for safety through Day 30. The planned sample size is based on the two sample t-test with an alpha level of 0.10 (one-sided), power of over 0.85, 30% to 50% higher reduction of DS-1040b compared to placebo in total thrombus volume, and

	standard deviation of 40%, in order to detect at least 50 % higher reduction at Cohort 1, 40 % at Cohort 2, 35% at Cohort 3 to 5, and 30% at Cohort 6.
Statistical Analyses:	Efficacy Analyses: The following key efficacy endpoints will be summarized and compared between the individual DS-1040b arms and pooled placebo arm: 1. Relative reduction (% reduction) in total thrombus volume from baseline to ≤ 12h from end of DS-1040b infusion assessed by CTA) in segmental or larger pulmonary arteries; 2. Proportion of subjects who achieve a ≥ 20% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion; 3. Proportion of subjects who achieve a ≥ 50% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion; The relative reduction (% reduction from baseline to ≤ 12h from end of infusion) in total thrombus volume of each DS-1040b dose will be compared with pooled placebo arm using two sample t-test statistics and p-value with no multiple comparisons adjustment. The proportions of subjects who achieve 20% and 50% relative reduction in total thrombus volume of each DS-1040b dose will be compared with pooled placebo arm using chi-square statistics and p-value with no multiple comparisons adjustment. The following secondary efficacy endpoints will be summarized and compared between DS-1040b arms and pooled placebo arm: 1. Recurrence of VTE (Composite of recurrent PE, new or recurrent DVT, VTE-related death; as well as the individual components) up to hospital discharge and up to Day 30 Visit; 2. Death, hemodynamic decompensation, or treatment escalation up to hospital discharge and up to Day 30 Visit; 3. Recurrence of PE up to hospital discharge and up

to Day 30 Visit;

4. MACE up to hospital discharge and up to Day 30 Visit.

Time to event data from randomization will be summarized by Kaplan-Meier methods.

Safety Analyses: Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. Aside from TEAEs and SAEs, safety measurements will include: physical examination findings, vital sign measurements, standard clinical laboratory parameters (including serum chemistry, hematology, urinalysis, cardiac biomarkers [proBNP and troponin], coagulation parameters), and electrocardiogram (ECG) parameters.

Values for safety assessments will be summarized by treatment group. Results from placebo-treated subjects will be pooled across cohorts.

Bleeding events will be summarized as ISTH major or CRNM bleeding by treatment. Results from placebo-treated subjects will be pooled across cohorts when comparing with DS-1040b treated subjects.

PK/PD Analyses: Descriptive statistics (sample size [N], number missing [N missing], arithmetic mean, standard deviation, coefficient of variation [%CV], minimum, maximum, and median) of DS-1040a plasma concentrations at each sampling time point and all PK parameters will be presented by treatment. In addition, the geometric mean and %CV for geometric mean will also be calculated for the PK parameters $AUC_{0\text{-}inf}$, AUC_{last}, C_{max}, and plasma concentration prior to end of continuous infusion.

Mean and median plasma concentration versus time data will be presented graphically for all treatments using original and semi-log scales.

Actual sampling times that differ from the scheduled sampling times by more than 5 minutes within the first hour, or by more than 30 minutes within the first 12 hours, or by more than 1 hour thereafter, will be listed but excluded from summary statistics and mean and median graphs.

The relationship between dose and exposure parameters

	(AUClast and AUC0-inf) will be examined graphically. Raw values for total TAFIa activity, TAFI antigen, clot lysis time, and D-dimer will be presented graphically by subject, and will also be summarized by time point and treatment. Change from baseline values (absolute value and percentage) will also be summarized. Pooled placebo data of all cohorts will be summarized.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACS	Acute Coronary Syndrome
AE	Adverse Event
AIS	Acute Ischemic Stroke
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
AV	Atrioventricular
BMI	Body Mass Index
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CRF	Case Report Form
CrCL	Creatinine Clearance
eCRF	Electronic Case Report Form
CRNM	Clinically Relevant Non-Major
CRO	Contract Research Organization
CSPV	Clinical Safety and Pharmacovigilance
CTA	Computed Tomography Angiography
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INN	International Non-proprietary Name
IRB	Institutional Review Board
ISTH	International Society of Thrombosis and Haemostasis
ITT	Intent-to-treat

ABBREVIATION	DEFINITION
IV	Intravenous
IxRS	Interactive Web/Voice Response System
LMW	Low Molecular Weight
MACE	Major Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified ITT
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamic
PE	Pulmonary embolism
PK	Pharmacokinetic
PPS	Per-Protocol Set
TEAE	Treatment-emergent Adverse Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAFI	Thrombin-Activatable Fibrinolysis Inhibitor
TAFIa	Activated form of TAFI
TEAE	Treatment-Emergent Adverse Event
t-PA	Tissue plasminogen activator
ULN	Upper Limit of Normal
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

1. INTRODUCTION

1.1. Background

Thrombin-activatable fibrinolysis inhibitor (TAFI) is a plasma procarboxypeptidase that, upon activation by thrombin, thrombinthrombomodulin complex or plasmin, turns into an antifibrinolytic enzyme termed activated form of TAFI (TAFIa). In a thrombus, TAFIa removes lysine residues at the carboxy terminal of fibrin degradation products, which prevents effective binding of plasminogen and tissue plasminogen activator (t-PA), resulting in impaired thrombolysis[2].

1.1.1. Data Summary

1.1.1.1. Nonclinical Studies

In vitro effects of DS-1040b on the human-, rat-, and monkey activated form of TAFI (TAFIa) were evaluated using plasma from each species. DS-1040b inhibited human, rat, and monkey TAFIa activity with the half maximal inhibitory concentration (IC50) values (95% confidence interval [CI] values) of 5.92 nmol/L (5.35 nmol/L to 6.55 nmol/L), 8.01 nmol/L (6.40 nmol/L to 10.0 nmol/L), and 4.48 nmol/L (3.53 nmol/L to 5.70 nmol/L), respectively.

The in vivo effect of DS-1040b on endogenous fibrinolytic activity was evaluated in a tissue factor-induced rat venous thromboembolism (VTE) model. DS-1040b increased plasma D-dimer levels in a dose-dependent manner, and the increase was significant at a dose of 0.063 mg/kg or more. The in vitro effect of DS-1040b on human platelet aggregation was evaluated in human platelet-rich plasma. Platelet aggregation inhibition up to the highest DS-1040b concentration used (100 μmol/L) was less than 50% for all agonists used. Moreover, based on additional in vitro studies, DS-1040b did not affect coagulation as measured by prothrombin time (PT) and activated partial thromboplastin time (aPTT). Also bleeding time was not impacted by DS-1040b administration in an in vivo rat tail bleeding time model where none of the DS-1040b doses investigated (3, 10, and 30 mg/kg) resulted in bleeding time prolongation, while recombinant tissue plasminogen activator (rt-PA) 5.2 mg/kg significantly prolonged bleeding time ± SEM from 300 ± 55 sec to 1350 ± 121 sec.

In single-dose toxicity studies in rats and cynomolgus monkeys DS-1040b induced acute toxicities (animal death) at high doses by bolus injection (300 mg/kg in rats and 1000 mg/kg in cynomolgus monkeys). DS-1040b did not induce detectable organ toxicity, genotoxicity, local irritation, or hemolysis in toxicity evaluation. The observed toxicities in the bolus injection studies are believed to be related to the acute increase in exposure after bolus injections. The no observed adverse effect level (NOAEL) was 220 mg/kg for rats and 66mg/kg for cynomologus monkeys, with no difference between sexes. The NOAEL in the 14-days repeated-dose intravenous (IV) bolus injection studies was 30 mg/kg/day for both rats and cynomolgus monkeys, with no differences between sexes. No deaths or test article related toxicities were observed in any of the groups. In the extended single-dose (0.5 hour short-term infusion followed by 24 hour continuous

infusion) toxicity studies the NOAEL was 220 mg/kg for rats and 66 mg/kg for cynomolgus monkeys, with no difference between sexes.

A 4-day continuous infusion toxicity study of DS-1040b was conducted in male and female F344/DuCrlCrlj rats. The NOAEL after a 4-day continuous intravenous infusion of DS-1040b in rats was considered to be 200 mg/kg/day for both males and females. There was no test article-related death or moribundity and no test article-related changes in clinical signs, body weight, food consumption, hematology, blood chemistry, necropsy, organ weight, or histopathology in any group.

Additional information on nonclinical studies is available in the Investigator's Brochure.[2]

1.1.1.2. Clinical Experience

Three clinical studies have been completed in humans with DS-1040b (DS1040-A-U101, DS1040-A- E102, and DS1040-A-U104) and the results are summarized below. Additional details are available in the Investigators Brochure[2].

The first-in-human study (DS1040-A-U101) was a Phase 1, single-blind placebo-controlled, randomized, 3-part, single-ascending dose study to assess the safety, tolerability, PK, and PD of DS-1040b in healthy young (18 to 45 years of age, inclusive) and elderly (65 to 75 years of age, inclusive) subjects. A total of 103 subjects were enrolled in this study which evaluated 2 dosing regimens: a 0.5-hour intravenous (IV) infusion (Part 1 and Part 2) and a 0.5 hour loading infusion followed by a 23.5-hour continuous infusion (Part 3). In Part 1 of the study, a total of 64 young subjects were enrolled in 8 dose cohorts of 8 subjects each (6 active and 2 placebo in each cohort). The doses of DS-1040b evaluated were 0.1, 0.2, 0.4, 0.8, 1.6, 3, 6, or 12 mg administered as 0.5-hour IV infusion. In Part 2 of the study, a total of 15 elderly subjects were enrolled in 2 dose cohorts: 7 subjects (6 active and 1 placebo) in a 3 mg dose cohort and 8 subjects (6 active and 2 placebos) in a 6 mg dose cohort. The doses of DS-1040b evaluated, 3 mg and 6 mg, were administered as a 0.5-hour IV infusion. In Part 3 of the study, a total of 24 young subjects were enrolled in 3 dose cohorts of 8 subjects each (6 active and 2 placebo in each cohort). The doses of DS-1040b evaluated were 10, 20, or 40 mg administered as a loading infusion of 10% of the total dose in 0.5 hours followed by a 23.5-hour continuous infusion.

The change in coagulation parameters PT, international normalized ratio (INR), aPTT, and fibrinogen from baseline were minor and not clinically significant; no clear dose related trends were noted. There was no clinically significant effect on platelet aggregation (performed with 10 µM adenosine 5' diphosphate and 0.5 mM arachidonic acid) at any dose level. In Part 1, an increase in bleeding time of 40% to 66% was observed on Day 1 at the end of infusion compared with Day -1 following DS-1040b doses of 3 mg, 6 mg, and 12 mg. All bleeding time values in Part 1 remained within the normal range (less than 10 minutes), and these changes in bleeding time were not considered significant. The bleeding time in Part 2 and Part 3 did not show any DS-1040b dose related trend. There were no clinically significant changes on any other safety laboratory parameters.

Plasma exposure of DS-1040a, a free form of DS-1040b, increased proportionally with increases in dose. Higher exposure levels were observed in elderly subjects compared with young subjects, which is due to prolonged systemic elimination. The mean half-life ($T_{1/2}$) in elderly subjects was longer than that in young subjects at corresponding doses. With 24-hour continuous infusion, by 12 hours after the end of infusion, plasma drug concentrations decreased to < 10% of the end-of-infusion concentration.

DS-1040b administration resulted in a dose-dependent decrease in TAFIa activity and 50% clot lysis time. A drug-related increase of D-dimer was also observed without clear dose dependency in healthy subjects. There were no changes in the level of TAFI antigen.

Overall, the DS-1040b doses were well tolerated in young and elderly subjects. The most common treatment-emergent adverse events (TEAEs) [experienced by ≥ 2 subjects] were contact dermatitis, dyspepsia, ecchymosis, and pain in extremity. All TEAEs were mild or moderate in severity. None of the moderate TEAEs were considered to be drug related. No deaths, drug-related serious adverse events (SAEs), or discontinuations were reported during the study.

In a Phase 1, open-label, single-dose, drug-drug interaction study (DS1040-E-102), the safety and tolerability of a single, IV dose of DS-1040b was assessed in healthy subjects after 5 days of aspirin treatment. A total of 18 subjects were enrolled in this study. Each subject received a loading dose of 300 mg aspirin on the morning of Day 1 followed by a daily dose of 75 mg aspirin on Days 2, 3, 4, and 5. On the morning of Day 5, the daily dose of aspirin was followed immediately by a 6-mg IV infusion of DS-1040b over 0.5 hours.

A single-IV dose of DS-1040b following 5 days of aspirin treatment was safe and well tolerated, with no new or unexpected safety concerns noted. The mean bleeding time increased following aspirin dosing from predose baseline to Day 4. There was no additional increase in mean bleeding time following co-administration of DS-1040b on Day 5.

Study DS1040-A-U104 was a Phase 1 study to evaluate the safety and tolerability of DS-1040b 20 mg IV infusion coadministered with enoxaparin 1 mg/kg subcutaneous in healthy subjects. Preliminary results indicate that coadministration of a single dose of enoxaparin 1 mg/kg SC injection with a single dose of DS-1040b 20 mg infused over 12 h in healthy subjects was safe and well tolerated. DS-1040a plasma concentrations and PK parameters were comparable when DS-1040b was administered alone or in combination with enoxaparin. Similarly, plasma enoxaparin (anti-FXa) levels and PK parameters remained comparable when enoxaparin was administered alone or with DS-1040b. DS-1040b administration led to a marked decrease in TAFIa activity which returned to baseline values within 36 hours after the end of the infusion. No further impact on TAFIa activity could be observed following coadiminstration of DS-1040b with enoxaparin. Administration of enoxaparin alone did not affect TAFIa activity. The most common TEAEs (experienced by ≥ 2 subjects) were at the injection site of enoxaparin and DS-1040b IV infusion site, which was reported following administration of enoxaparin or enoxaparin with DS-1040b, and headache, which was reported after administration of enoxaparin with DS-1040b. No spontaneous bleeding or bruising

occurred. All TEAEs reported during the study were mild. No apparent effect of DS-1040b or enoxaparin or their combination on aPTT could be observed.

1.2. Study Rationale

DS-1040b is an inhibitor of TAFIa intended for use in the treatment of thrombotic diseases including VTE and acute ischemic stroke (AIS).

Venous thromboembolism, which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with a high morbidity and if left untreated, may progress to a fatal outcome. Venous thromboembolism is a common disorder with estimated annual incidence of approximately 2 to 3 per 1000 individuals. Of the 2 components PE has more severe consequences as it is associated with increased mortality rates for up to 3 months after the index PE event. There are more than 100 000 cases annually in the US of PE with as many as 25% of patients experiencing sudden death[3,4]. Anticoagulant therapy is the mainstay of therapy for subjects with acute VTE, with the main objective to prevent thrombus extension and further embolization, (both early and late recurrences). The classical management of subjects with VTE in the US consists of an initial treatment with body weight-adjusted subcutaneous (SC) low molecular weight heparin, adjusted-dose IV or fixed-dose SC unfractionated heparin (UFH), or body weight-adjusted SC fondaparinux, followed by long-term treatment with an oral vitamin K antagonist (VKA) or a novel oral anticoagulant (NOAC)[5]. Systemic or catheter-directed fibrinolytic therapy is used for treatment of massive PE and for management of selected patients with submassive PE, whereas catheter-directed fibrinolytic therapy is used in some patients with extensive iliofemoral DVT. Clinical trial data in patients with PE showed that thrombolysis was associated with lower risk of recurrence of PE. In patients with intermediate-risk PE, the benefit of reduced mortality associated with thrombolysis is offset by increased risk of major bleeding events[4]. Limitations of existing antithrombotic drugs have prompted a search for novel agents[6]. DS-1040b, a tosylate salt of DS-1040a, is a low molecular weight compound that is under development by Daiichi Sankyo Inc. as an injectable formulation. DS-1040b inhibits enzymatic activity of TAFIa and enhances thrombolytic activity triggered by endogenous or exogenously administered t-PA. Therefore, DS-1040b is expected to enhance the effect of t-PA and to provide a novel antithrombotic therapy in VTE and AIS without increasing bleeding risk.

1.3. Risks and Benefits for Study Subjects

No clinical studies have been conducted in human subjects to evaluate the efficacy of DS-1040b. However, the results from nonclinical studies suggest treatment with DS-1040b may enhance fibrinolysis in thromboembolic disease.

No anticipated risks of DS-1040b have been established. Overall, IV infusion of DS-1040b was safe and well tolerated in healthy young and elderly subjects. All TEAEs in the 3 completed Phase 1 clinical studies were mild or moderate in severity. None of the moderate TEAEs were considered to be drug related. No deaths, drug-related SAEs, or discontinuations were reported in the completed clinical studies.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

The primary objective of this study is to evaluate the safety and tolerability using bleeding as the primary endpoint. Secondarily, this study will serve as a proof-of-concept by evaluating the effect that DS-1040b administration has on total thrombus volume reduction from baseline to the end of infusion, assessed by contrast enhanced computed tomography scan (CT angiography or CTA). This study will also evaluate the pharmacokinetic/pharmacodynamic (PK/PD) and biomarker activity of DS-1040b in subjects with acute PE and the correlation with imaging.

2.1.1. Primary Objectives

The primary objective of the study is to assess the safety and tolerability of ascending doses of DS-1040b given as a single IV infusion over 12, 24, 48 and 72 hours, respectively, when added to standard of care (SOC) anticoagulation therapy, compared to placebo by evaluating the rate of clinically relevant bleeding (International Society of Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major bleeding [CRNM]).

2.1.2. Secondary Objectives

The secondary objectives include the following:

1. Relative reduction (% reduction) in total thrombus volume from baseline to ≤ 12h from end of DS-1040b infusion, assessed by CTA in segmental or larger pulmonary arteries;
2. Proportion of subjects who achieve a ≥ 20% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion and compared to placebo;
3. Proportion of subjects who achieve a ≥ 50% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion and compared to placebo;
4. Recurrence of VTE (Composite of recurrent PE, new or recurrent DVT, VTE-related death; as well as the individual components) up to hospital discharge and up to Day 30 Visit after dosing;
5. Death, major cardiovascular events ([MACE]: defined as a composite of cardiovascular death, non-fatal myocardial infarction, stroke, or systemic embolic events [SEE]), hemodynamic decompensation, treatment escalation (defined as catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter) up to hospital discharge and up to Day 30 Visit after dosing;
6. Overall safety evaluation (SAEs, TEAEs, clinical laboratory parameters);

7. Pharmacokinetics of DS-1040b in subjects with PE;
8. Assess the PD effect of DS-1040b on TAFIa activity, TAFI antigen and D-dimer fibrinolysis biomarkers, in subjects with PE.

2.1.3. Exploratory Objectives

Assess the effect of DS-1040b on clot lysis as a biomarker for TAFIa activity in subjects with PE.

2.2. Study Hypothesis

Results from nonclinical studies suggest treatment with DS-1040b may enhance fibrinolysis in thromboembolic disease. In healthy subjects IV administration of DS-1040b in doses up to 40 mg over 24 hours was well tolerated and resulted in dose-dependent decreases in TAFIa activity and 50% clot lysis time as well as drug-related increases in D-dimer, but with no clear dose dependency.

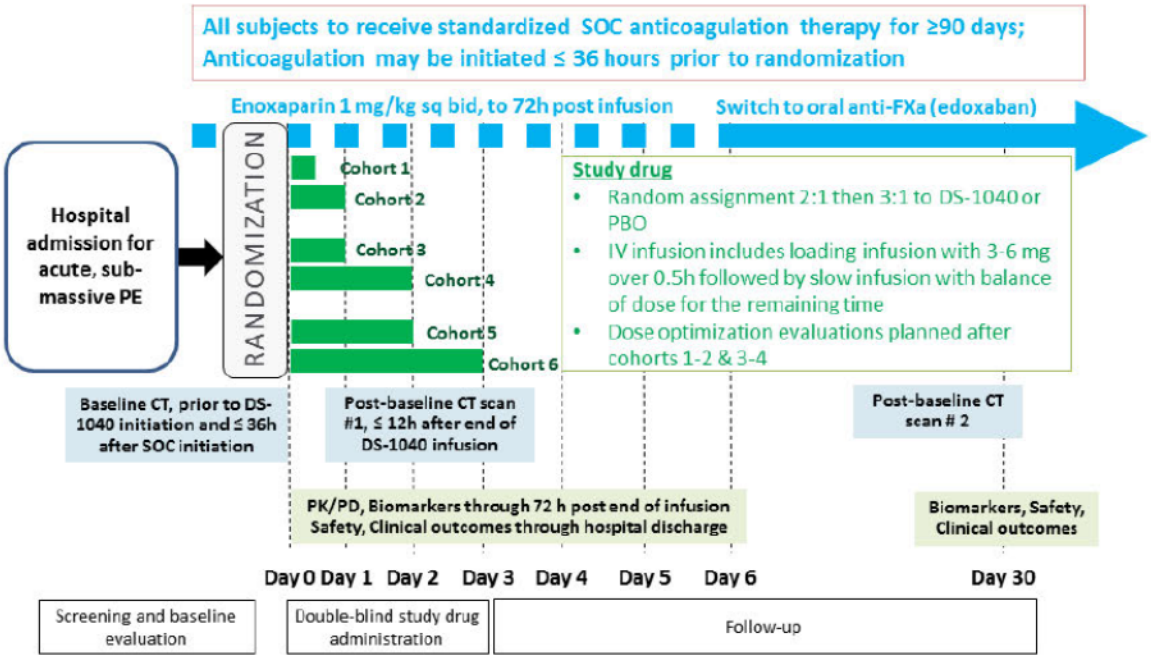
This study will test the hypothesis that in subjects with acute PE characterized as low-risk, intermediate-risk, or submassive, treated with SOC anticoagulation therapy, adding DS-1040b, given at a dose that provides complete inhibition of TAFIa activity, will result in a greater reduction in total thrombus volume from baseline to the end of the study drug infusion, with no increase in clinically relevant bleeding, when compared to placebo.

3. Y GN

3.1. Overall gn

This will be a randomized, double-blind, placebo-controlled, multi-center, s ngle-ascending dose study ects with acute PE characterized as low-risk or intermediate- ubm sive PE. A graphical representation of t is provided in Figure 3.1.

Figure 3.1:



3.2. ion Study Design

s udy ıptive design and o s x s q scending-e cohorts, organized in three pairs (1-2, 3-1 5-6). Up to a on e ıtions are planned t e h ıd pair of cohorts. nt m dose opt ua ons ; of imaging, om he study aims to also identify a range of DS-40b doses e e inhibition of TAFI activity and to estimate e optimal i such doses in order to achieve c ni l a ıgful reductions in total thrombus volume.

Subjects must be hospitalized for acute PE categorized as low risk, or intermediate-risk, or submassive PE, have CTA confirmation of PE lesions in a segmental or larger pulmonary artery, and not have systemic thrombolytic or catheter-based therapy planned in order to be considered for inclusion. Subjects should be in otherwise satisfactory health in the opinion of the Investigator and may be already on LMW (Heparin) at randomization, provided that it was started within 36 hours of randomization.

At the time of randomization, eligible subjects must initiate or be transitioned to the study-specified enoxaparin regimen. After randomization, the subjects will receive an IV infusion with blinded study drug (either DS-1040b or placebo) over a period of time ranging from 12h to 72h depending on the cohort. The infusion duration will be the same for all subjects enrolled within each cohort (Table 3.1). The assignment to either active drug or placebo will be blinded to the subjects and study site staff who may come in direct contact with the subjects as well as to the Sponsor and Medpace study team. Following the end of study drug infusion the administration of enoxaparin will continue for an additional 72h to continue to provide a uniform therapeutic background while PK/PD sample collection is completed and an adequate washout period before subjects are switched to the oral anticoagulant, which in this study will be edoxaban. Enoxaparin administration and PK/PD sample collection after the end of study drug infusion may be done in an ambulatory setting if subjects are discharged home.

Efficacy will be evaluated by measuring reduction in total thrombus volume from baseline to ≤ 12h post end of blinded study drug infusion using imaging data, therefore confirmation of measurable PE lesion(s) by CTA scan in a segmental or larger pulmonary artery is mandatory prior to randomization. In order to be included in the efficacy evaluation, subjects will have to successfully complete the IV infusion with blinded study drug and have valid, interpretable CTA scans, at both baseline and at the end of the IV infusion. A second post-baseline CTA scan is planned at Day 30. All CTA scans will be read centrally by the Core Imaging Laboratory, which will identify the number and size of individual pulmonary lesions at segmental and higher pulmonary artery level and calculate total thrombus volume. The imaging method will be validated using the data generated from the first 10 subjects in Cohort 1 according to the validation plan to be developed by the Core Imaging Laboratory. Should the first validation fail, data from the next 10 subjects enrolled in either Cohorts 1 or 2 will be used to validate the method.

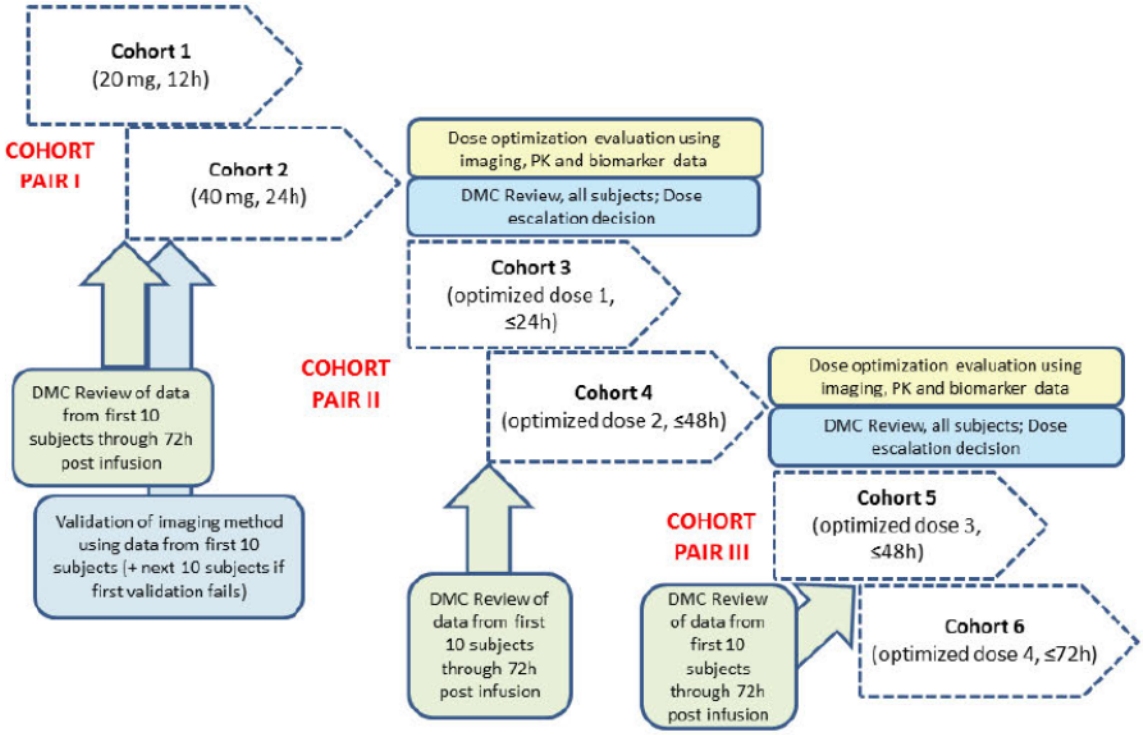
An independent, unblinded, Data Monitoring Committee (DMC) will review key safety parameters for each cohort and provide its endorsement for the continuation of the study and the dose escalation decisions. This study may be terminated at any time for safety reasons upon advice of the DMC. An independent, blinded Clinical Events Committee (CEC) will be established to classify bleeding events, which are the primary endpoint in this study. The details on the roles and responsibilities of both DMC and CEC will be provided in their respective charters.

In Cohorts 1 and 2 eligible subjects will be randomized in a 2:1 ratio to either DS-1040b or placebo. Beginning with Cohort 3 the randomization ratio will change to 3:1.

Study enrollment will be done in pairs of cohorts, beginning with Cohorts 1 and 2, followed by Cohorts 3 and 4, then 5 and 6. Within each pair of cohorts, subject enrollment will be staggered for safety, ie, enrollment in Cohorts 2, 4, and 6 will begin

after the first 10 subjects in C s ly completed
d have reached 72 urs he 1 (when the
t measurements ends) without any increase in e primary
safety endpoint (levant bleeding) he e is emerging,
s d b t nde nt, unblinded DMC. ol e temporarily
suspended while ations are ongoing (Figure 3.2).

Figure 3.2: Cohort osing and Dose Optimization Scheme



Up to two dose evaluations are planned in this study il include
safety, imaging (total us volume s l post end of
infusion), PK marker data ubj t w h post end of
blinded study drug infusion. The first one will include subjects from s 1-2 and the
second from Cohorts 1-4. Tl i z i ne the total
ura on of a ninistration to be used in Cohorts 3-4 and rts 5-6,
respectively. The dose optim rri i linded
fashion by a designated a .

e f infusion for each cohort are shown in Table 3.1. The total
t d tration for Cohorts 1-2, a 2h and
40 24h, re . T be a n erated in
healthy subjects, both young n y c e ition of
TAFIa activity (Study DS- 040-A-U101). The estimated to a ation of

administration for Cohorts 3-6 are shown as ranges since they will be chosen based on the results of the two planned dose optimization evaluations.

Table 3.1: Dosing Ranges and Infusion Duration by Cohort

Cohort	Total Dose[1] (mg)	Total Duration of Blinded Study Drug Infusion	Loading Infusion over 0.5 h		Maintenance Infusion	
			Dose (mg)	Duration	Dose (mg)	Duration
1	20	12 h	3	0.5 h	17.0	11.5 h
2	40	24 h	3	0.5 h	37.0	23.5 h
DOSE OPTIMIZATION EVALUATION BASED ON IMAGING AND BIOMARKER DATA						
3	>40-≤80[1]	24 h	3-6	0.5 h	37-74.0	23.5 h
4	>40-≤120[1]	48 h	3-6	0.5 h	37-114.0	47.5 h
DOSE OPTIMIZATION EVALUATION BASED ON IMAGING AND BIOMARKER DATA						
5	>40-≤160[1]	48 h[2]	3-6	0.5 h	37-154	47.5 h
6	>40- ≤180[1]	72 h[2]	3-6	0.5 h	37-154	71.5 h

[1]Total doses for cohorts 3, 4, 5 and 6 will be multiples of the optimal dose calculated based on the results of the interim dose optimization evaluation planned after Cohorts 2 and 4, respectively.
[2]The final duration for Cohorts 5 and 6 will be chosen based on the results of the dose optimization evaluations planned after Cohorts 2 and 4, respectively.

Simulated PK profiles for the first two cohorts are shown in Table 3.2. The simulations were conducted using a population PK model established from the earlier single-ascending dose study in healthy young and elderly subjects (Study DS1040-A-U101), assuming a linear PK for DS-1040b over the doses to be assessed. Simulated PK values shown in Table 3.2 refer to those in typical subjects with body weight of 75 kg and creatinine clearance (CrCL) of 60 and 90 mL/min, respectively.

Table 3.2: Simulated PK Profiles for Cohorts 1 and 2

Cohort	Dosing Regimen			CrCL (mL/min)	Simulated Plasma PK Parameters			
	Total Dose	Loading Dose	Maintenance Dose		$C_{0.5}$ ng/mL	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng*hr/mL)
1	20 mg	3 mg/0.5 h	17 mg/11.5h	60	243	301	12	4797
				90	238	255	12	3935
2	40 mg	3 mg/0.5 h	37 mg/23.5 h	60	243	338	24	9594
				90	238	284	24	7869

3.3. Stopping Rules

Stopping rules and or criteria to stop or modify dose escalation during the study will be specified in the DMC charter.

4. STUDY POPULATION

This study will enroll subjects hospitalized for acute PE characterized as low-risk, intermediate-risk, or submassive for whom the plan is to be treated with SOC anticoagulation therapy alone.

4.1. Inclusion Criteria

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

1. Male or female subjects, age 18 to 75 years and body weight between 50 and 120 kg, inclusive;
2. Subjects admitted to hospital with a clinical diagnosis of acute PE categorized as low risk or intermediate-risk or submassive PE and for whom catheter-based therapy is not planned;
    a. Subjects must have a CTA scan confirming the PE diagnosis and with at least one measurable index lesion in a segmental or larger pulmonary artery prior to randomization;
    b. Subjects should be in otherwise satisfactory health in the opinion of the Investigator;
    c. Subjects may have concurrent DVT and have an inferior vena cava (IVC) filter placed prior to randomization;
    d. Subjects may already be on SOC low molecular weight [LMW] (Heparin) at the time of randomization but for no longer than 36 hours.
3. Able to provide written informed consent.

4.2. Exclusion Criteria

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

1. Subjects with acute PE categorized as high-risk or massive, or who are hemodynamically unstable, evidenced by a heart rate > 120 /min and a systolic blood pressure (SBP) of < 90 mmHg for more than 15 consecutive minutes or a drop in SBP of > 40 mmHg since presentation;
2. Subjects for whom use of a thrombolytic, either systemic or via catheter, is planned;
3. Subjects with PE lesions only in the sub-segmental or smaller arteries, which due to limitations of the imaging method may not be consistently identified and measured;
4. Subjects unable or unwilling to take the study-sourced SOC anticoagulation therapy;

5. Subjects receiving any VKAs prior to randomization or receiving more than 36 hours treatment with LMW(Heparin) in therapeutic doses prior to randomization;
6. Subjects who had prior intracranial hemorrhage, known arteriovenous malformation or aneurysm, or evidence of active bleeding;
7. Subjects with a platelet count < 100,000, INR > 1.7, or an elevated partial thromboplastin time;
8. Subjects who within 48 hours of randomization have used an anti-Factor IIa agent such as dabigatran or an anti-FXa agent such as rivaroxaban, apixaban, or edoxaban;
9. Subjects with history of endocarditis;
10. Subjects with < 6 month history of acute coronary syndrome (ACS) whether or not they have undergone percutaneous coronary intervention (PCI);
11. Subjects who require ongoing dual antiplatelet therapy or treatment with aspirin alone in a dosage of more than 100 mg/per day;
12. 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;
13. Subjects with uncontrolled hypertension at randomization, evidenced by systolic blood pressure > 180 mm Hg or diastolic blood pressure>120 mmHg, or who require parenteral medication to maintain blood pressure below these limits;
14. Subjects who within 3 months prior to randomization have had intracranial surgery, clinically significant head trauma (in the opinion of the Principal Investigator), a stroke, or have received thrombolytic treatment;
15. Subjects with ECG evidence of 2nd degree or higher atrioventricular (AV) block or with QTcB or QTcF >450 ms;
16. Subjects who within 21 days prior to randomization have had gastrointestinal or genitourinary bleeding;
17. Subjects who within 14 days prior to randomization have had major surgery or a lumbar puncture (or epidural steroid injection);
18. Subjects with hemoglobin < 10 g/dL;
19. Subjects with an estimated glomerular filtration rate (using Modification of Diet in Renal Disease equation) < 60 mL/min/1.73 m^2;
20. Subjects with diagnosed active liver disease or with elevation of liver enzymes/bilirubin:
    a. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 2 times upper limit of normal (ULN)
    b. Total bilirubin (TBL) ≥ 1.5 times ULN (except due to confirmed Gilbert's syndrome)

21. Subjects with known history of testing positive for Hepatitis B antigen or Hepatitis C antibody before randomization;
22. Subjects with known history of testing positive for the human immunodeficiency virus (HIV);
23. Subjects with active malignancy (diagnosed within 5 years) except for adequately treated non-melanoma skin cancer or other non-invasive or in-situ neoplasm (eg, cervical cancer in situ);
24. Subjects undergoing chemotherapy or radiation therapy in the 30 days prior to randomization or expected to initiate such therapy during study participation;
25. Subjects with congestive heart failure;
26. Subjects with chronic obstructive pulmonary disease;
27. Female subjects of child bearing potential with a positive pregnancy test or who are lactating, or unwilling to use reliable means of contraception (physical barrier, patient or partner) in conjunction with a spermicidal product, contraceptive (pill, patch, injectable), or intrauterine devices (IUDs) following treatment period and through the Day 30 final follow-up visit;
28. Subjects currently participating in another investigational study or who have participated in an investigational drug study within 30 days or prior to randomization;
29. Subjects unlikely to comply with the protocol (eg, uncooperative attitude, inability to return for subsequent visits, and/or otherwise considered by the investigator to be unlikely to complete the study);
30. Subjects with any condition (including laboratory abnormalities) that, in the opinion of the Investigator, would potentially place the subject at increased risk of harm through participation in this study.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)

Open-label, background SOC anticoagulation regimen:

All subjects included in this study regardless of the cohort or the treatment arm to which they are randomized will receive SOC anticoagulation per the current guidelines for treatment of patients with acute PE, to ensure an effective therapeutic background. Due to the early stage of development and in order to minimize variability the anticoagulation regimen for this study was standardized for all subjects to enoxaparin 1mg/kg, subcutaneous q12h for 5 days (6 days for Cohort 6) followed by edoxaban 60 mg (30 mg for subjects requiring dose adjustment), per oral once daily for the remainder of the study, through Day 30. Both enoxaparin and edoxaban will be provided by the Sponsor as open label and will be used according to their approved local label for this indication. Subjects must be on the standardized, study-sourced enoxaparin at the time of randomization, before the blinded study drug administration may begin. The duration of the enoxaparin administration of 5 days for Cohorts 1-5 and 6 days for Cohort 6 is dictated by the need to provide a uniform anticoagulation background during the infusion with blinded study drug (ranging from 12 to 72h) and for an additional 72 hours following the end of the study drug infusion to allow the PK/PD sample collection to complete and to provide an adequate washout period before the switch to the oral anticoagulant.

Following the end of the study, Savaysa®/Lixiana® (edoxaban, per oral, once daily) will be made available at no cost to the patients for at least 90 days, at the investigator's discretion per the current treatment guidelines[1].

Double-blind treatment groups:

Within each cohort subjects already receiving the study-sourced SOC enoxaparin will be randomized to one of the following two treatment groups:

1. DS-1040b, or
2. DS-1040b placebo

5.1.2. Method of Treatment Allocation

Subjects will be randomized to the study by registering the subject in the Interactive Voice/Web Response System (IxRS). At randomization, the appropriate site personnel will contact the IxRS to randomize subject to the appropriate treatment cohort. IxRS will provide a unique subject identification number, allocate the treatment group assignment within the cohort for the subject and provide the appropriate drug supply number(s). A fax or e-mail will be sent by the IxRS to provide the appropriate cohort assignment and drug supply.

5.1.3. Blinding

The randomization schedule will be produced by a statistician from the Biostatistics CRO, according to the specifications provided by the Sponsor statistician. A dummy schedule will be produced before the study start and will be checked by the Sponsor statistician. After approval of the dummy schedule, the Biostatistics CRO will modify the random generator and issue the final randomization to a Sponsor statistician not involved in this study, who will approve the final randomization.

Randomization will be blinded to the subjects, Investigators, Sponsor (Daiichi Sankyo) study team, and CRO (Medpace) and ARO (ITREAS) staff.

The dose optimization evaluation(s) will be carried out in an unblinded fashion by a separate, designated team with the appropriate firewalls in place to prevent accidental unblinding of the study team.

5.1.4. Emergency Unblinding Procedure

In the case of an emergency where, in the opinion of the Investigator, discontinuation of study drug infusion is not sufficient and the study treatment must be unblinded in order to evaluate further a course of medical treatment, the Investigator can perform the unblinding by directly accessing the IxRS.

In the event of an emergency unblinding, the subject will be informed about their treatment assigned. Information about the treatment assignment **must be** restricted to designated study center staff/ personnel who are providing immediate care to the subject. Any documentation of the treatment assignment **must be** maintained separately (ie, in a secured file). The information **must not be** included in the subject's source files to ensure the treatment assignment will remain blinded to all other parties at the site and from the CRO not involved with the subject's immediate care.

When an emergency unblinding has occurred, an automatic notification (via e-mail) will be sent to the investigator and selected Daiichi Sankyo Inc. study personnel from the IxRS vendor. The notification will not contain any unblinding information. This will trigger the follow-up process to document the unblinding by completing the Emergency Unblinding by Investigator Form (to be provided by study personnel upon receipt of IxRS notification) and submission to Daiichi Sankyo Inc. Clinical Safety and Pharmacovigilance (CSPV); please refer to the form for completion instructions.

5.2. Study Drug(s)

5.2.1. Description

The Investigational Products (IP) for this study are:

- DS-1040b (10 mg/10mL)
- DS-1040b placebo (0.9% sodium chloride injection)

All subjects will receive background SOC anticoagulation therapy per the current standard of care for patients with acute PE, which for this study will include enoxaparin for 5 days (6 days for Cohort 6) followed by edoxaban through the end of study visit at

Day 30. Both will be provided as open label and used in accordance to their approved label. The administration of the IP will take place while subjects are receiving enoxaparin, which will continue for an additional 72h after the end of the IV infusion with blinded study drug. Following the end of the study, Savaysa®/Lixiana® (edoxaban, per oral, once daily) will be made available at no cost to the patients for at least 90 days, at the investigator's discretion per the current treatment guidelines[1].

5.2.2. Labeling and Packaging

DS-1040b Injection 10 mg/10 mL will be provided in a clear glass vial. Details of the packaging and labeling of DS-1040b Injection 10 mg/10 mL will be provided in the pharmacy manual.

Enoxaparin will be supplied in pre-filled syringes.

Savaysa®/Lixiana® (edoxaban) 60 mg and 30 mg tablets will be provided in 30 count bottles.

Packaging and labeling will be performed in accordance with Good Manufacturing Practice.

5.2.3. Preparation

DS-1040b Injection 10 mg/10 mL and placebo will be prepared according to the detailed procedures for drug preparation that are provided in the pharmacy manual by an unblinded member of the site staff.

5.2.4. Administration

DS-1040b Injection 10 mg/10 mL vial will be transferred into IV infusion solution (0.9% Sodium Chloride Injection, USP). The placebo for DS-1040b will be 0.9% Sodium Chloride Injection, USP which will be sourced at the site.

The blinded solution containing either DS-1040b or placebo will be administered as a single, continuous IV infusion. The IV infusion will consist of an initial loading dose of 3-6 mg (depending on the cohort) administered as a 0.5 hour infusion followed by a maintenance dose with the balance of the total dose administered over the remaining time for the respective cohort (11.5h for Cohort 1, 23.5h for Cohorts 2 and 3, up to 47.5h for Cohorts 4 and 5, and up to 72h for Cohort 6).

The DS-1040b total doses for Cohorts 1 and 2 are 20 mg over 12h and 40 mg over 24h, respectively. These doses have been shown in healthy volunteers to be safe and well tolerated and to provide an almost complete inhibition of TAFI activity. Up to two dose optimization evaluations are planned using imaging, PK/PD, and biomarker data from Cohorts 1-2 and 1-4, respectively, to optimize the total dose of DS-1040b and infusion duration for the remaining cohorts.

Background anticoagulation therapy per the current SOC will be standardized across all study sites and subjects to enoxaparin 1 mg/kg subcutaneous, every 12 hours for 5 days (6 days for Cohort 6) followed by edoxaban 60 mg (30 mg for subjects requiring dose adjustment), per oral, once daily, through the end of study visit, at Day 30. Both

enoxaparin and edoxaban will be provided as open label and used in accordance to their approved labels. Following the end of the study, Savaysa®/Lixiana® (edoxaban, per oral, once daily) will be made available at no cost to the patients for at least 90 days, at the Investigator's discretion per the current treatment guidelines[1].

5.2.5. Storage

Drug supplies must be stored in a secure, limited access storage area under the labeled storage conditions:

- DS-1040b Injection 10 mg/10 mL should be stored up to 25°C (excursions permitted up to 30°C);
- DS-1040b IV solution in-use stability will be provided in the pharmacy manual.

In the event of an excursion from storage requirements, the site will quarantine the Investigational Product and the Sponsor will determine whether the Investigational Product can be used.

Lovenox (enoxaparin) and Savaysa®/Lixiana® (edoxaban) should be stored in accordance to their label instructions.

5.2.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, and sign the Receipt of Shipment Form provided. Receipt of shipment should be made by contacting the IxRS. The original Receipt of Shipment Form will be signed and retained at the site.

In addition, the Investigator or designee shall contact Medpace personnel as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the study drug. The record must be kept current and should contain the dates and quantities of study drug received, subject's identification number for whom the study drug was dispensed, the date and quantity of study drug dispensed and remaining, as well as the initials of the dispenser.

At the end of the study, or as directed, all DS-1040b, including unused, partially used, or empty containers, will be destroyed at the site. In the event a site cannot destroy the DS-1040b, it will be returned to a designee as instructed by Sponsor. Investigational Product will be destroyed or returned only after the study monitor has completed a final inventory to verify the quantity to be destroyed or returned. The return of Investigational Product must be documented and the documentation included in the shipment. At the end of the study, a final Investigational Product reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the Investigator when approved in writing by Sponsor and Sponsor has received copies of the site's drug handling and disposition Standard Operating Procedures (SOPs).

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

5.3. Control Treatment

The control in this study will be placebo because for patients with acute PE characterized as low risk, intermediate-risk, or submassive, which is the population targeted for inclusion in this study, the current SOC does not provide any other treatment options besides anticoagulation.

All subjects participating in this study will receive SOC anticoagulation therapy as per the current treatment guidelines for patients with acute PE, to ensure an effective therapeutic background. Due to the early stage of development and in order to limit variability, the background anticoagulation regimen used in this study will be standardized for all subjects to enoxaparin, 1 mg/kg, subcutaneous, every 12 hours for up to 6 days followed by Savaysa®/Lixiana® (edoxaban) 60 mg (30 mg for subjects requiring dose adjustment) (per oral once daily) through the end of study visit, at Day 30. After discontinuation of the enoxaparin, the first dose of Savaysa®/Lixiana® should be taken at the next scheduled administration of enoxaparin[7,8]. The administration of DS-1040b or placebo via IV infusion will take place while study subjects are being treated with enoxaparin. Both enoxaparin and edoxaban will be provided as open label and used in accordance to their approved labels. Following the end of the study, Savaysa®/Lixiana® (edoxaban, per oral, once daily) will be made available at no cost to the patients for at least 90 days, at investigator's discretion per the current treatment guidelines[1].

5.4. Dose Interruptions and Reductions

Subjects may interrupt the IV infusion with blinded study drug at any time due to safety reasons and in these cases study drug administration should be permanently discontinued. Please refer to Section 5.7.1 for additional information. Short interruptions to address IV line blockage are permitted.

Dose reductions are not permitted for study drug in this study.

5.5. Method of Assessing Treatment Compliance

All subjects in this study will receive the IV infusion with DS-1040b or placebo as hospital inpatients and under nursing supervision.

Since DS-1040b and placebo IV infusions will be administered at the site, treatment compliance will not be monitored in this study. However, the time of administration and dose amount will be captured for each subject. Administration of study drug will be recorded in the eCRF.

Enoxaparin and edoxaban will be used in accordance with their respective labels and per the SOC to provide a uniform and effective anticoagulation regimen for all subjects in this study. Since enoxaparin will be administered at the site or by a visiting nurse at the subject's home, treatment compliance will not be measured. However, the date and time

of administration and dose amount will be captured for each subject in the electronic case report form (eCRF). Similarly the date and time when the edoxaban therapy is initiated will be recorded in the eCRF.

5.6. Prior and Concomitant Medications

During study drug administration and for the specified number of days following the completion of study drug infusion or upon early withdrawal, the following medications are not allowed:

- Antiplatelet agents (aspirin, clopidogrel): After 24 hours post-study drug administration, use of antiplatelet agent will be at the discretion of the Principal Investigator.
- Any thrombolytic agent, used either systemically or catheter-directed for at least 72 hours after the end of study drug infusion.

During the study, concomitant medications required to treat TEAEs will be permitted. Other concomitant medications for pre-existing conditions (ie, hypertension, diabetes, etc.) are permitted, unless otherwise specified above. Concomitant medication usage will be at the discretion of the Principal Investigator.

Any medication (other than study drug) taken by subjects during the course of the study will be recorded and coded using the World Health Organization (WHO) drug dictionary.

5.7. Subject Withdrawal/Discontinuation

5.7.1. Reasons for Withdrawal

Temporary interruptions in the administration of study drug infusions, other than brief ones to address a blocked IV line, are not allowed in this study. If a subjects needs to interrupt administration of the study drug infusion, then study drug administration must be permanently discontinued. The reason for the study drug discontinuations will be recorded in the eCRF. A subject may discontinue study drug for a number of reasons including those listed below.

- Reasons Related to adverse events (AEs):
  - Initiating or continuing study drug places the subject at undue hazard as determined by the Investigator;
  - SAE or other safety concern that is related to study drug treatment;
  - Major life-threatening bleeding (per ISTH definition);
- Withdrawal by Subject
- Physician Decision
- Death
- Protocol Deviation
- Study Terminated by Sponsor

- Other

5.7.2. Withdrawal Procedures

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

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

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

- Obtain supine vital sign assessments;
- Perform a 12-lead ECG in triplicate;
- Obtain blood samples for safety laboratory assessments (serum chemistry and hematology);
- Collect urine sample for urinalysis;
- Urine pregnancy test;
- Assess subject for AEs;
- Record concomitant medications.

5.7.3. Subjects Lost to Follow-up

If a subject becomes lost to follow-up, the sites will be given instructions on actions to take to try to locate the subject.

6. STUDY PROCEDURES

A schematic study visit schedule is provided in Appendix 17.1.

6.1. Study Qualification/Pre-Randomization

The subject will be hospitalized during this period.

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 informed consent form (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 pre-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;
- Assess inclusion/exclusion criteria (see Section 4.1 and Section 4.2);
- Review medical history;
- Review any prior and concomitant medications;
- Ensure that the subject has a diagnosis of PE in a segmental or larger artery confirmed by appropriate imaging methods;
- Ensure that the subject qualifies with regard to the laboratory tests for exclusion criteria (see Section 4.2):

Samples taken 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 48 hours of randomization. Alternatively, the central laboratory may be utilized for the above study qualification laboratory tests.

- Full documentation for the above study qualification procedures and related results are required, including local laboratory results used to qualify the subject.

6.2. Day 0: Baseline Visit

The subject continues to be hospitalized during this period.

- Register the subject in the Interactive Voice/Web Response System (IxRS)
- Record any prior and concomitant medications (confirm that subject did not begin treatment with LMW heparin earlier than 36 hours prior to dosing);
- Assess subjects for AEs;
- Perform physical examination, including weight;
- Obtain supine vital sign assessments;
- Perform a 12-lead ECG in triplicate;
- Obtain blood samples for central laboratory safety assessments (serum chemistry and hematology, see Section 9.8 and Appendix 17.2)
- Obtain blood sample for Coagulation Panel (see Section 9.8 and Appendix 17.2) ;
- Obtain a urine sample for central laboratory urinalysis (see Section 9.8 and Appendix 17.2);
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential. The pregnancy test will be performed with either serum or urine samples following standard practice at the site;
- Obtain PK blood samples (see Section Section 8.1 and Appendix 17.2);
- Obtain PD blood sample (see Section Section 8.2 and Appendix 17.2);
- Record CT scan for thrombus measurement;
- Initiate or transition subject to the study-specified enoxaparin regimen;
- Start the study drug infusion.

An optional PGx sample can be obtained at any time after dosing.

6.3. Day 1-3: Double-Blind Treatment Period

The subject continues to be hospitalized during this period. The following procedures are to be performed at the end of the blinded study drug infusion:

- Record any prior and concomitant medications;
- Assess subjects for AEs;
- Obtain supine vital sign assessments;
- Perform a 12-lead ECG in triplicate;
- Obtain Coagulation Panel blood samples;
- Obtain PK blood samples;

- Obtain PD blood samples;
- Record CT scan for thrombus measurement (no more than 12 hours after the end of infusion).

6.4. Day 4-6: 72 hour After End of Infusion Follow-up

- Record any prior and concomitant medications;
- Assess subjects for AEs;
- Obtain supine vital sign assessments;
- Perform a 12-lead ECG in triplicate (optional);
- Obtain blood samples for safety laboratory assessments (serum chemistry and hematology) within 12 hours after the end of infusion or at the time of discharge;
- Obtain a urine sample for urinalysis within 12 hours after the end of infusion or at the time of discharge;
- Obtain Coagulation Panel blood samples;
- Obtain PK blood samples;
- Obtain PD blood samples.

Subjects must remain hospitalized during study drug infusion (DS-1040 or placebo) and may be discharged any time after the end of study drug infusion CT scan is obtained, at the Investigator's discretion. However, it will be necessary for subjects to continue anticoagulation treatment with enoxaparin, until switching to edoxaban, as well as to obtain PK/PD samples from subjects for an additional 72 hours post-study drug infusion. This may be accomplished by keeping the subject hospitalized for the additional time needed, or using home nursing services if the subject is discharged before completing these study procedures.

6.5. Day 30 ± 3 days: Long term Follow-up Period

This visit will be performed in an outpatient setting.

- Record any prior and concomitant medications;
- Assess subjects for AEs;
- Obtain supine vital sign assessments;
- Perform physical examination;
- Record CT scan for thrombus measurement.

7. EFFICACY ASSESSMENTS

7.1. Primary Efficacy Endpoint(s)

- Relative reduction (%reduction) in total thrombus volume from baseline to ≤ 12h from end of DS-1040b infusion assessed by CTA) in segmental or larger pulmonary arteries;
- Proportion of subjects who achieve a ≥ 20% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion;
- Proportion of subjects who achieve a ≥ 50% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion.

7.2. Secondary Efficacy Endpoint(s)

- Recurrence of VTE (Composite of recurrent PE, new or recurrent DVT, VTE-related death; as well as the individual components) up to hospital discharge and up to Day 30 Visit;
- Death, hemodynamic decompensation, or treatment escalation (defined as catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or thrombus fragmentation by catheter) up to hospital discharge and up to Day 30 post randomization;
- MACE (defined as a composite of cardiovascular death, or non-fatal myocardial infarction, stroke, or SEE) up to hospital discharge and up to Day 30 Visit.

7.3. Exploratory Efficacy Endpoint(s)

Evaluation of TAFIa activity using clot lysis as a biomarker.

7.4. Appropriateness of Selected Efficacy Endpoint(s)

In order to assess the objective of anticoagulant therapy to prevent thrombus extension and further embolization, the relative reduction in total thrombus volume, defined as from baseline to ≤ 12h from end of DS-1040b infusion, was selected as key efficacy endpoint. Since there is no evidence of DS-1040b effects on reduction in total thrombus volume for subjects with acute PE characterized as low-risk or intermediate-risk or submassive PE, both continuous and dichotomous evaluations will be conducted.

Furthermore, to detect any signals for efficacy on clinical endpoints, recurrence of VTE, death, hemodynamic decompensation, or treatment escalation, and MACE up to hospital discharge and up to Day 30 Visit will be assessed.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

Blood samples for PK/PD analyses will be obtained at the timepoints specified in the Schedule of Events (Appendix 17.1). Instructions for the handling of blood samples and shipping of plasma samples for PK/PD analyses are included in the separate laboratory manual. The actual time of study drug administration and the exact time of blood sampling for PK analysis must be recorded on the eCRF.

Plasma concentrations of DS-1040a will be determined by a validated liquid chromatography – tandem mass spectrometry method. Details about the assay method and validation results are included in a separate document prepared by the bioanalytical laboratory.

8.1. Pharmacokinetic (PK) Endpoint(s)

Blood samples for PK assessment will be collected in each cohort at the following time points:

- **Cohort 1**: 0, 0.5 (immediately prior to end of loading infusion), 3, 6, 12 (immediately prior to end of maintenance infusion), 18, 24, 48, and 72 hours
- **Cohorts 2 and 3**: 0, 0.5 (immediately prior to end of loading infusion), 6, 12, 24 (immediately prior to end of maintenance infusion), 36, 48, 72, and 96 hours
- **Cohorts 4 and 5**: 0, 0.5 (immediately prior to end of loading infusion), 12, 24, 48 (immediately prior to end of maintenance infusion), 60, 72, 96, and 120 hours
- **Cohort 6**: 0, 0.5 (immediately prior to end of loading infusion), 12, 24, 48, 72 (immediately prior to end of maintenance infusion), 84, 96, 120, and 144 hours

PK sampling scheme for Cohorts 3-6 is provisional, which may be modified depending on the optimal dose/regimen to be chosen.

The following PK parameters will be calculated from the plasma concentrations of DS-1040a using noncompartmental analysis:

- area under concentration-versus-time curve, from time 0 to the last quantifiable concentration sampling point (AUC_{last});
- maximum (peak) observed plasma concentration (C_{max});
- time of maximum observed concentration (T_{max});
- plasma concentration immediately prior to the end of continuous infusion

If data permit, the following parameters will be estimated:

- the area under the concentration-versus-time curve, from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$);
- elimination half-life ($T_{1/2}$);
- clearance (CL).

8.2. Pharmacodynamic (PD) Endpoint(s)

Blood samples for PD assessment of total TAFIa activity, TAFI antigen, D-dimer, and clot lysis will be collected in each cohort at the following time points:

- **Cohort 1**: Baseline (predose), 0.5 (end of loading infusion), 6, 12 (end of maintenance infusion), 24 and 48 hours
- **Cohorts 2 and 3**: Baseline (predose), 0.5 (end of loading infusion), 24 (end of maintenance infusion), 36, 48, and 72 hours
- **Cohorts 4 and 5**: Baseline (predose), 0.5 (end of loading infusion), 48 (end of maintenance infusion), 60, 72, and 96 hours
- **Cohort 6**: Baseline (predose), 0.5 (end of loading infusion), 72 (end of maintenance infusion), 84, 96, and 120 hours

Pharmacodynamic analysis for total TAFIa activity, D-dimer, TAFI antigen and clot lysis (an exploratory biomarker) will be performed. Remaining blood samples will be used for post-hoc analyses for biomarkers that are involved in TAFI pathways or disease-related pathways to better understand the action of TAFIa inhibition, therapeutic response or disease progression. Instructions for the analyses will be covered in a separate document prepared by the respective analytical laboratories.

8.3. Biomarker Endpoint(s)

See Section 8.2 above.

8.4. Immunogenicity

Not applicable.

8.5. Pharmacogenomic Analysis

As part of this study, a single 4 mL blood sample will also be collected for pharmacogenomic (PGx) analysis. Deoxyribonucleic acid (DNA) biomarkers will be examined to evaluate the relationship between TAFI-related and/or disease-related genes and response to the study drug, and/or the therapeutic response to the disease condition (eg, VTE). In addition, the relationship between TAFI-related and/or disease-related genes and disease condition (eg, VTE) will be explored. All participants should be presented with the PGx ICF at randomization. Participation in this portion of the study is optional for all subjects. Thus, those who choose not to provide a sample for PGx analysis may still participate in the main portion of the study.

The blood PGx sample should be collected for subjects who sign the PGx ICF after dosing.

As emerging information regarding the safety and efficacy of DS-1040b may become available in the future, samples will be retained for possible future research. The sample will be retained until the DNA has been exhausted or until the Sponsor instructs the genotyping contractor to destroy the sample in accordance with laboratory procedures. During this time, the DNA sample will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time as long as there is DNA remaining.

To ensure subject confidentiality, sample tubes will be identified only by a barcode label. This barcode will be linked to the subject's identification number.

Instructions for sample collection, preparation, handling, storage, and shipment will be provided in a separate manual.

9. SAFETY EVALUATION AND REPORTING

9.1. Adverse Event Collection and Reporting

All clinical AEs (see Section 9.4.1 for definitions) occurring after the subject signs the ICF and up to the Day 30 follow-up visit, whether observed by the investigator or reported by the subject, will be recorded on the Adverse Event CRF page. 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 AEs and SAEs are to be reported according to the procedures in Section 9.5.

All laboratory results, vital signs, and ECG results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

At each visit, the investigator 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.

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

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures or treatments requiring hospitalization for pre-existing conditions that 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.

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.

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

As Daiichi Sankyo Inc. is the Market Authorization Holder for edoxaban, SAEs reported during the 30-day follow-up period should indicate in the event narrative whether the events are attributed to edoxaban therapy, which is provided as the NOAC per SOC; these events are subject to regulatory reporting requirements for a marketed product. After study completion, all events observed with edoxaban therapy should be reported as spontaneous cases to Daiichi Sankyo Inc. per contact information on the product label.

9.2. Safety Endpoint Event(s)

9.2.1. Bleeding

The primary safety endpoint in this study is:

- Clinically relevant bleeding (defined as major or CRNM bleeding).

Bleeding definitions (per ISTH[9]) are provided below:

Major bleeding is defined as clinically overt bleeding with one or more of the following:

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

Clinically relevant non-major (CRNM) bleeding is defined as overt bleeding not meeting the criteria for major bleeding but eg, requires medical attention or is associated with discomfort for the subject such as pain, or impairment of activities of daily life.

All other overt bleeding episodes not meeting the criteria for major or CRNM bleeding will be classified as nuisance bleeding.

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.

9.3. Events of Special Interest

No events of special interest have been defined for this study.

9.4. Adverse Event

9.4.1. Definition of Adverse Event

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and that 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

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

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

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (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:

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

9.4.3. Severity Assessment

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

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

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

9.4.4. Causality Assessment

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

- 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).

or

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

9.4.5. Action Taken Regarding Study Drug(s)

No dose modifications (increases or reductions) are permitted in this study and neither are interruptions in the administration of the IV infusion with blinded study drug longer than to address a blocked IV line (Section 5.7.1) Therefore the choices for action taken with the study drug in this study are limited to the following:

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.

- Dose Increased: The dosage of study drug was increased.
- Not Applicable: Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment

9.4.6. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or over-the-counter (OTC) medication was required to treat the adverse event.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

9.4.7. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the adverse event with no residual effect observed.
- Recovering/Resolving
  - The adverse event improved but has not fully resolved.
- Not Recovered/Not Resolved
  - The adverse event itself is still present and observable.
- Recovered/Resolved with Sequelae
  - The residual effects of the adverse event are still present and observable.
  - Include sequelae/residual effects.
- Fatal
  - Fatal should be used when death is a direct outcome of the adverse event.
- Unknown

9.5. Serious Adverse Events Reporting–Procedure for Investigators

All AEs and SAEs will be reported in the CRF/eCRF. All SAEs must be reported on a Daiichi Sankyo Inc. Serious Adverse Event Report (SAVER) form within 24 hours of awareness, and using the designated fax transmittal form.

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. A detailed

narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. All SAEs reported during the 30-day follow-up period should indicate in the event narrative whether the events are related to edoxaban therapy. Source documents (including medical reports) will be retained at the study center and should not be submitted to the Sponsor for SAE reporting purposes.

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.

Please call the local SAE Hotline (see Study Manual) or your study monitor for any questions on SAE reporting.

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

Daiichi Sankyo Inc. and/or Medpace will inform Investigators, Institutional Review Boards/Ethics Committees (IRBs/ECs), and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study centers or other Daiichi Sankyo Inc. studies of the investigational drug, as appropriate per local reporting requirements.

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

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

9.7. Exposure In Utero During Clinical Studies

Daiichi Sankyo Inc. must be notified of any subject who becomes pregnant while receiving study medication or up to the last safety follow-up visit (30 ± 3 days after the last administration of study medication or withdrawal from the study, whichever occurs later).

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 and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for

immediate classification as a SAE (ie, post-partum complications, spontaneous or induced 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.

9.8. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

Although it is permissible to use local lab results to qualify subjects for randomization to the study if done as part of routine care outside the auspices of this study, lab samples will be collected at baseline and subsequent to randomization for testing by a central laboratory.

- Serum chemistry, hematology and urinalysis samples will be collected at baseline and within 12 hours after completing study drug infusion or at the time of discharge (see Appendices Section 17.1 and Section 17.2).
- Coagulation Parameters: PT, aPTT, INR and fibrinogen will be assessed at baseline (predose), end of loading infusion, end of maintenance infusion and 24 hours after the end of infusion (see Appendix 17.2), as follows:
  - **Cohort 1**: predose, 0.5 (end of loading infusion), 12 (end of maintenance infusion), and 48 hours
  - **Cohorts 2 and 3**: predose, 0.5 (end of loading infusion), 24 (end of maintenance infusion), and 48 hours
  - **Cohorts 4 and 5**: predose, 0.5 (end of loading infusion), 48 (end of maintenance infusion), and 72 hours
  - **Cohort 6**: predose, 0.5 (end of loading infusion), 72 (end of maintenance infusion), and 96 hours
- Serum or urine pregnancy test (for women of childbearing potential). The pregnancy test will be performed with either serum or urine samples following standard practice at the site;

The procedures for sample collection for analysis by the central laboratory will be defined in a study laboratory manual. The results will be reviewed and compared with the central laboratory's normal ranges.

All laboratory values must be appraised by the Investigator as to clinical significance. All abnormal laboratory values considered clinically significant by the Investigator must be recorded in the adverse event page of the eCRF. Abnormal laboratory values occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer considered clinically significant.

9.9. Vital Signs

Vital sign measurements will include systolic blood pressure, diastolic blood pressure, and heart rate.

9.10. Electrocardiograms

Standard supine 12-lead ECGs will be performed by qualified technicians in triplicate on the ECG machine dedicated to this study. Electrocardiograms will be reviewed at the site for treatment of any urgent issues. The clinical significance of any ECG change must be assessed by the Investigator in the context of the subject's medical history, physical examination, and concomitant medications. The Investigator or delegated physician will review, sign, and date all ECGs.

9.11. Physical Examinations

A complete physical examination, with the exception of the genitourinary system and prostate, will be performed on each subject at baseline and at the follow up visit on Day 30. Body weight will be measured (or best estimated if not feasible to measure) for all subjects at study qualification/pre-randomization.

9.12. Other Examinations

See Section 10.

10. OTHER ASSESSMENTS

Imaging Evaluations:

Three contrast-enhanced CT scans are planned in this study, at baseline, within 12 hours after the end of study drug infusion and at Day 30 ± 3, to evaluate the effect of study drug administration on the thrombus size/volume. In order to be randomized in this study subjects must have a baseline CT scan confirming the PE diagnosis and with at least one measurable index lesion in a segmental or larger pulmonary artery. Details regarding the imaging evaluations including the validation of the method may be found in the Imaging Acquisition Manual for site developed and provided by the Core Imaging Laboratory.

11. STATISTICAL METHODS

Detailed statistical methods will be described in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock.

11.1. Analysis Sets

Safety Analysis Set: Safety analysis set will include all subjects who received at least 1 dose of the Investigational Product.

Efficacy Analysis Set: Efficacy analysis set will include all subjects in the safety analysis set who have valid CT imaging evaluations at both the baseline and at the 12h post-end of infusion time points and has successfully completed administration of the study drug infusion.

PK Analysis Set: PK analysis set will include all subjects in the safety analysis set who have at least 1 PK sample with measurable concentration of DS-1040a.

PD Analysis Set: PD analysis set will include all subjects in the safety analysis set who have at least 1 post dose PD assessment.

11.2. General Statistical Considerations

All quantitative efficacy, PK, PD, and safety data will be tabulated with descriptive summary statistics: arithmetic mean; standard deviation (SD); median, minimum and maximum values; number of observations. In addition, geometric mean and geometric coefficient of variation (CV) % will be provided for $AUC_{0\text{-}inf}$, AUC_{last}, and C_{max} values. Frequency counts and percentages will be provided for categorical data. Summaries will be provided for each dose arm and on the pooled placebo arm. When data are available for both pre-dose and post dose assessments, summaries will be provided on pre-dose assessments, post dose assessments, and change from pre-dose to post dose assessments, respectively.

11.3. Study Population Data

Subject disposition will be summarized for each treatment group and in total for the safety analysis set. The number of subjects for each defined analysis set by treatment group as well as in total population will also be tabulated.

The demographic and baseline characteristics will be summarized descriptively for the safety analysis set. Continuous demographic variables (age [calculated from date of birth to the date of dose], weight, height, and body mass index [BMI]) for all subjects will be summarized with descriptive statistics. Categorical demographic variables (sex, race, and ethnicity) will be summarized with frequency counts and corresponding percentages.

Study drug exposure and study duration will be summarized using descriptive statistics by treatment group for the safety analysis set.

11.4. Statistical Analysis

11.4.1. Efficacy Analyses

Efficacy parameters will include total thrombus volume, recurrence of VTE, death, MACE, hemodynamic decompensation, and treatment escalation.

Efficacy analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

Values for efficacy assessments will be summarized by treatment group. All placebo-treated subjects will be pooled across cohorts as one group in the summary of efficacy results.

11.4.1.1. Primary Efficacy Analyses

The following primary efficacy endpoints will be summarized and compared between DS-1040b arms and pooled placebo arm:

- Relative reduction (% reduction) in total thrombus volume from baseline to ≤ 12h from end of DS-1040b infusion assessed by CTA in segmental or larger pulmonary arteries;
- Proportion of subjects who achieve a ≥ 20% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion;
- Proportion of subjects who achieve a ≥ 50% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to ≤ 12h from end of DS-1040b infusion.

The relative reduction in total thrombus volume of each DS-1040b dose will be compared with pooled placebo arm using two sample t-test statistics and p-value with no multiple comparisons adjustment.

The proportions of subjects who achieve 20% and 50% relative reduction in total thrombus volume of each DS-1040b dose will be compared with pooled placebo arm using chi-square statistics and p-value with no multiple comparisons adjustment.

11.4.1.2. Secondary Efficacy Analyses

The following secondary efficacy endpoints will be summarized and compared between DS-1040b arms and pooled placebo arm:

- Recurrence of VTE (Composite of recurrent PE, new or recurrent DVT, VTE-related death; as well as the individual components) up to hospital discharge and up to Day 30 Visit after dosing;
- Death, hemodynamic decompensation, or treatment escalation up to hospital discharge and up to Day 30 Visit after dosing;
- Recurrence of PE up to hospital discharge and up to Day 30 after dosing;
- MACE up to hospital discharge and up to Day 30 Visit after dosing.

Time to event data from randomization will be summarized by Kaplan-Meier methods.

11.4.1.3. Exploratory Efficacy Analyses

The following endpoints will be summarized and compared by between DS-1040b arms and pooled placebo arm:

- Relative reduction (% reduction) in total thrombus volume from baseline to Day 30 Visit from end of DS-1040b infusion assessed by CTA in segmental or larger pulmonary arteries;
- Proportion of subjects who achieve a ≥ 20% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to Day 30 Visit;
- Proportion of subjects who achieve a ≥ 50% greater relative reduction in total thrombus volume assessed by CTA in segmental or larger pulmonary arteries, from baseline to Day 30.

The relative reduction in total thrombus volume of each DS-1040b dose will be compared with pooled placebo arm using two sample t-test statistics and p-value with no multiple comparisons adjustment.

11.4.2. Pharmacokinetic/Pharmacodynamic Analyses

11.4.2.1. Pharmacokinetic Analyses

Descriptive statistics (sample size [N], number missing [N missing], arithmetic mean, standard deviation, coefficient of variation [%CV], minimum, maximum, and median) of DS-1040a plasma concentrations at each sampling time point and all PK parameters will be presented by treatment. In addition, the geometric mean and %CV for geometric mean will also be calculated for the PK parameters $AUC_{0\text{-}inf}$, AUC_{last}, C_{max} and plasma concentration prior to end of continuous infusion.

Mean and median plasma concentration versus time data will be presented graphically for all treatments using original and semi-log scales.

Actual sampling times that differ from the scheduled sampling times by more than 5 minutes within the first hour, or by more than 30 minutes within the first 12 hours, or by more than 1 hour thereafter, will be listed but excluded from summary statistics and mean and median graphs.

The relationship between dose and exposure parameters (AUC_{last} and $AUC_{0\text{-}inf}$) will be examined graphically.

11.4.2.2. Pharmacodynamic Analyses

Raw values for total TAFIa activity, TAFI antigen, clot lysis time, and D-dimer will be presented graphically by subject, and will also be summarized by time point and treatment. Change from baseline values (absolute value and percentage) will also be summarized. Pooled placebo data of all cohorts will be summarized.

11.4.2.3. Biomarker Analyses

Not applicable.

11.4.2.4. Pharmacogenomic Analyses

Exploratory PGx analyses for the potential predictive benefits of DS-1040b may be assessed later in a separate report.

11.4.3. Safety Analyses

Safety parameters will include SAEs, TEAEs, physical examination findings, vital signs measurements, standard clinical laboratory parameters, bleeding events, and ECG parameters.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

Values for safety assessments will be summarized by treatment group. All placebo-treated subjects will be pooled across cohorts as one group in the summary of safety results.

11.4.3.1. Adverse Event Analyses

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (latest version). All AEs, including SAEs, will be mapped to system organ class and preferred term and will be listed in the data listing. A TEAE is defined as an AE that emerges during treatment, having been absent pretreatment, or worsening relative to the pre-treatment state. The number and percentage of subjects reporting TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment. The TEAEs will be further summarized by severity and relationship to study drug. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs leading to discontinuation of study treatments.

A by-subject AE (including treatment-emergent) data listing including but not limited to verbatim term, preferred term, system organ class, severity, and relationship to study treatment will be provided. Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study treatments, will be listed.

11.4.3.2. Clinical Laboratory Evaluation Analyses

Hematology, serum chemistry, urinalysis, and coagulation at each planned assessment and change from baseline at each planned post-baseline assessment will be summarized for the safety analysis set by treatment. Shift tables (in categories of low, normal, and high, when appropriate) will be provided for each treatment, as well. Subjects with abnormal values will be noted in the data listings.

11.4.3.3. Vital Sign Analyses

Vital sign evaluations at each planned assessment and change in vital sign values from baseline at each planned post-baseline assessment will be summarized for the safety analysis set by treatment.

11.4.3.4. Electrocardiogram Analyses

The ECG parameters (PR, RR, QRS, QT, QT interval corrected (QTc) using Bazett's formula [QTcB], and Fridericia's formula [QTcF]) and heart rate at each planned assessment will be summarized by treatment. The QT intervals will be corrected for heart rate by the Bazett's and Fridericia's formula (QTcB = QT/[RR]1/2 and QTcF = QT/[RR]1/3 respectively). The incidence of outliers in absolute QT, QTcF and QTcB intervals (> 450 ms, > 480 ms, and > 500 ms), and the change from predose baseline in QT, QTcF and QTcB intervals (> 30 ms and > 60 ms) for triplicate ECGs will be summarized by treatment.

11.4.3.5. Physical Examination Analyses

Physical examination data at each evaluation will be listed. Subjects with clinically significant abnormal findings will be noted in the data listings.

11.4.3.6. Bleeding Events Analyses

Bleeding events will be summarized as ISTH major or CRNM bleeding by treatment. Results from placebo-treated subjects will be pooled across cohorts when comparing with DS-1040b treated subjects.

Time to event data for the bleeding events from randomization will be analyzed by Kaplan-Meier methods.

11.4.4. Other Analysis

Up to two dose optimization evaluations are planned in this study, which will include safety, imaging (total thrombus volume reduction from baseline to 12 hours post end of infusion), pharmacokinetic and select biomarker data from subjects who reach 72h post end of blinded study drug infusion. The first one will include subjects from Cohorts 1-2 and the second from Cohorts 1-4. These dose optimization evaluations will determine the total doses and the duration of administration to be used in Cohorts 3-4 and Cohorts 5-6, respectively. The dose optimization evaluation will be carried out in an unblinded fashion by a designated team. Subject enrollment will be temporarily suspended while these evaluations are ongoing. Details for these analyses will be provided in a separate, dedicated statistical analysis plan.

11.5. Interim Analyses

No interim analysis has been planned.

11.6. Sample Size Determination

Approximately 22 subjects will be enrolled per cohort, to yield at least 18 evaluable subjects for Cohort 1-2 and at least 20 for Cohort 3-6 with a total of 118 evaluable subjects. The randomization ratios of DS-1040b to placebo are 2:1 for Cohorts 1 - 2 and of 3:1 for Cohorts 3-6. A subject will be deemed evaluable if he/she has valid CT imaging evaluations at both baseline and at the ≤12h post-end of infusion and has successfully completed administration of the blinded study drug infusion. Randomized

subjects who do not complete the blinded study drug administration (ie, subjects who stop the IV infusion early due to AEs) will still be followed for safety through Day 30.

The planned sample size is based on the two sample t-test with an alpha level of 0.10 (one-sided), power of over 0.85, 30% to 50% higher reduction of DS-1040 compared to placebo in total thrombus volume, and standard deviation of 40%, in order to detect at least 50 % higher reduction at Cohort 1, 40 % at Cohort 2, 35% at Cohort 3 to 5, and 30% at Cohort 6.

11.7. Statistical Analysis Process

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and clinical study conclusions.

The statistical software SAS Version 9.3 or higher will be used to analyze the data.

12. DATA INTEGRITY AND QUALITY ASSURANCE

12.1. Monitoring and Inspections

The Daiichi Sankyo Inc. monitor/designee 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, CRFs, source data, and other pertinent documents).

The verification of 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 will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study site. The monitor is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator and will ensure that appropriate action (s) 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 to the satisfaction of the Sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of study center facilities (eg, pharmacy, drug storage areas, laboratories) 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. The Investigator should respond to audit findings. In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

All relevant observations and data related to the study, as per the study protocol, will be recorded on eCRF pages. A representative of Daiichi Sankyo Inc. or their designee will provide instruction for completing the eCRF. Adequate and accurate case records should be maintained, including the evaluation of inclusion and exclusion criteria, medical history, physical examinations, clinical assessments, a record of clinical safety laboratory sample collection, drug administration, AEs, and final evaluation.

The eCRF data entry shall be completed within 72 hours of the visit. The investigator must electronically sign and date the eCRF. The signature shall indicate that the investigator has reviewed the data and data queries recorded on eCRFs and the site notifications, and agrees with the content. After the completion of the study, eCRFs including audit trail will be returned to Daiichi Sankyo Inc. and stored in the archives.

The Investigator will receive a copy of their site's eCRFs including audit trail on electronic media.

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 study centers, a Clinical Data Management review will be performed on subject data according to specifications given to Sponsor or designee. Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the electronic data capture (EDC) application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies. To resolve any questions arising from the Clinical/Data Management review process for paper CRFs, data queries, and/or study center notifications will be sent to the study center for completion and return to the Sponsor/Medpace; whereas, CRFs queries will be raised and resolved within the EDC application. In addition, the data will be reviewed for adherence to the protocol and GCP. For eCRFs, the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the electronic data capture (EDC) application and also resolved within the EDC application.

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

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

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

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 CRFs will be included on the Signature List.

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

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

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

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

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study drug, 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 study center (Trial Master File). 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 study center 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.

12.5. Record Keeping

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

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

All essential documentation will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation region and until there are no pending or contemplated marketing applications in an International Conference on Harmonisation region or at least 2 years have lapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

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

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

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 the Sponsor. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

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

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

14. PUBLICATION POLICY

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics and Regulatory Compliance

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

- European Commission Directive (2001/20/EC Apr 2001) and/or;
- European Commission Directive (2005/28/EC Apr 2005) and/or;
- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March, 1997 and/or;
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 of 25 November, 2014;
- Other applicable local regulations.

15.2. Subject Confidentiality

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

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

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

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be

given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

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

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

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

For studies in the US, an additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA). Also, a separate special consent will be required for pharmacogenomic testing for this protocol.

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator Brochure, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the EC 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 SAP.

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

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study

initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after approval by the relevant regulatory bodies.

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

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

15.5. Protocol Deviations

The investigator 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 IRBs/ECs.

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

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

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

If applicable, the Investigator should notify the EC or IRB of deviations from the protocol in accordance with local procedures.

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

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

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

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

15.7. Protocol Amendments

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

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

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

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

15.8. Study Termination

This study may be terminated at any time for safety reasons upon advice of the DMC.

In addition, key safety parameters, including the primary endpoint (adjudicated clinically relevant bleeding, defined as ISTH major or clinically relevant non-major bleeding) as well as other relevant safety information, such as SAEs and panic laboratory values will be monitored in real time, in a blinded fashion, by the study team as per the study-specific medical monitoring plan and the DMC will receive reports from this team.

Subject enrollment is planned in three pairs of cohorts with two interim evaluations to optimize the doses using safety, efficacy, and pharmacokinetic/biomarker data. As an added measure of safety subject enrollment within each pair of cohorts will be staggered Enrollment in the second cohort of the pair will begin only after DMC has reviewed the data of the first 10 subjects from the first cohort of the pair have cleared the 72h post end of infusion time point, and there was no increase in clinically relevant bleeding nor other major safety concerns.

15.9. Data and Safety Monitoring Board

The primary role for the DMC will be to examine the unblinded safety and efficacy data (bleeding events, SAEs, VTE, and MACE) in an ongoing manner and alert the of the study leadership team in case of any clinically concerning safety issues.

In addition they will review:

a. key safety parameters (eg, clinically relevant bleeding, SAEs and panic laboratory values) of the first 10 subjects from the first cohort of each pair after the subjects cleared the 72h post end of infusion time point), and

b. safety and efficacy data (bleeding, serious adverse events (SAE), VTE and major cardiovascular events (MACE) events) of each cohort in order to allow for a balanced advice regarding safety /efficacy and to provide recommendation related to the continuation of the study and the dose escalation decisions.

The DMC may recommend that the study be stopped at any time for any safety reasons.

Further details on the roles and responsibilities will be described in the DMC Charter.

15.10. Address List

15.10.1. Sponsor

Daiichi Sankyo Inc.
399 Thornall Street
Edison, NJ 08837
[redacted]

15.10.1.1. Sponsor Medical Monitor

[redacted]
Senior Director, Clinical Development (Cardiovascular)
Daiichi Sankyo Inc.
399 Thornall Street
Edison, NJ 08837
[redacted]

15.10.1.2. Sponsor Clinical Study Leader

[redacted]
Senior Director, Clinical Development (Cardiovascular)
Daiichi Sankyo Inc.
399 Thornall Street
Edison, NJ 08837
[redacted]

15.10.1.3. Sponsor Clinical Operations Delivery Lead

[redacted]
Senior Clinical Study Manager
Clinical Development, Operations
Daiichi Sankyo Inc.
399 Thornall Street
Edison, NJ 08837 • USA
[redacted]

15.10.2. ITREAS

[redacted]
Honthorstsraat 2-A
1071 DD Amsterdam
Netherlands.
[redacted]

[redacted]

15.10.3. CROs

Medpace Inc.
5375 Medpace Way
Cincinnati, Ohio 45227
USA
[redacted]

15.10.4. Drug Safety

15.10.4.1. Medpace: DSPD Serious Adverse Event Reporting Form General Contact

Medpace SAE hotline – USA:

[redacted]

Medpace SAE hotline – Europe:

[redacted]

15.10.5. Data Management

[redacted]
Manager, Data Management, Biostatistics and Data Operations
Daiichi Sankyo Inc.
399 Thornall Street
Edison, NJ 08837 • USA
[redacted]

15.10.6. Central Laboratory

Medpace Reference Laboratories, LLC

5365 Medpace Way

Cincinnati, OH, 45227

15.10.7. Imaging/Core Lab Vendor

[redacted]
Mount Sinai School of Medicine
1428 Madison Ave., Atran Bldg. 8th Floor, Room 829
New York, NY 10029
[redacted]

[redacted]

15.10.8. IxRS Vendor

Medpace, Inc.

5375 Medpace Way

Cincinnati, OH, 45227.

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17. APPENDICES

17.1. Schedule of Events

Table 17.1: Schedule of Events

	Study Qualification/Pre-Randomization	Baseline[a]	Double-Blind Treatment Period	72 hour After End of Infusion Follow-Up	Long term Follow-Up Period[b]
Day		**0**	**1 - 3**	**4 – 6[c]**	**30**
Hour	**≤ 36**	**0**			
Visit Window (days)					+/-3
Informed consent	X				
Inclusion/exclusion criteria	X				
Medical history	X				
Prior and concomitant medication[d]	X	X	X	X	X
Serum/urine pregnancy test		X			
Genotyping sample			X[e]		
Weight		X			
Physical examination		X			X
Vital signs (supine)		X	X	X	X
Electrocardiogram (12-lead in triplicate)[f]		X	X	X	
Serum chemistry		X		X[g]	
Hematology		X		X[g]	
Urinalysis		X		X[g]	
Coagulation Panel (see Section 9.8 and Appendix 17.2)		X	X	X	

	Study Qualification/Pre-Randomization	Baseline[a]	Double-Blind Treatment Period	72 hour After End of Infusion Follow-Up	Long term Follow-Up Period[b]
Day		**0**	**1 - 3**	**4 – 6[c]**	**30**
Hour	**≤ 36**	**0**			
PK Sampling (see Section 8.1 and Appendix 17.2)		X	X	X	
PD Sampling (see Section 8.2 and Appendix 17.2)		X	X	X	
CTA for thrombus volume		X	X[h]		X
Adverse event monitoring[i]		----------X----------			
Drug administration		X			
Hospital Stay	----------X----------				

aPTT = activated partial thromboplastin time; CTA = computed tomography angiography; INR = International Normalized Ratio; PT = prothrombin time; PK = pharmacokinetic; TAFIa = thrombin-activatable fibrinolysis inhibitor.

[a] All procedures performed prior to dosing.
[b] Follow-up at 30 day ± 3 will be conducted in an outpatient setting.
[c] End of infusion follow-up begins with discontinuation of study drug and continues until Day 4 to Day 6 depending on the dosing cohort.
[d] Must include start of LMW heparin no more than 36 hours prior to randomization.
[e] May be performed at any timepoint postdose.
[f] ECG to be performed at baseline and then within 12 hours of end of infusion; optional ECG at hospital discharge.
[g] Lab sample (including urinalysis) collected within 12 hours of end of infusion or at the time of discharge.
[h] CT to be performed no more than 12 hours after end of infusion.
[i] Collection of non-serious AEs, SAEs, including clinical outcome events, will continue through Day 30.

17.2. Listing of Laboratory Assays

The total blood volume that will be drawn from each subject ranges between 120-141 mL. The variations are due to differences in the total number of PK and PD samples to be collected during study drug treatment and after study drug administration is stopped based on dosing cohort.

Test	Volume per test (mL)	Number of Timepoints per Subject	Total Volume (mL)
Baseline / Predose			
Serum chemistry, serum pregnancy (All Cohorts)	7	1	7
Hematology (All Cohorts)	3	1	3
Coagulation Panel (All Cohorts)	6	1	6
PK Panel (All cohorts)	3	1	3
PD Panel (All cohorts)	4.5 x 2	1	9
Genotyping (optional)	4	1	4
Treatment Period			
Coagulation Panel (All Cohorts)	6	2	12
PK Panel (Cohorts 1-5)	3	4	12
PK Panel (Cohort 6)	3	5	15
PD Panel (Cohort 1)	4.5 x 2	3	27
PD Panel (Cohorts 2-6)	4.5 x 2	2	18
Postdose			
Serum chemistry (All Cohorts)	7	1	7
Hematology (All Cohorts)	3	1	3
Coagulation Panel (All Cohorts)	6	1	6
PK Panel (All Cohorts)	3	4	12
PD Panel (Cohort 1)	4.5 x 2	2	18
PD Panel (Cohorts 2-6)	4.5 x 2	3	27

Serum Chemistry Panel

- Sodium, Potassium, Chloride, Bicarbonate, Total Protein, Albumin, Calcium, Magnesium, Phosphorous, Serum Glucose, BUN, Uric Acid, CK, ALT, AST, ALP, Creatinine, CrCl, Total Bilirubin (Direct & Indirect)

Hematology Panel

- RBC and WBC count, MCH, MCHC, MCV, Hgb, Hct, Differential (% and/or Absolute Values for Neutrophils, Lymphocytes, Monocytes, Eosinophils and Basophils), Platelet count

Coagulation Panel

- INR, PT, aPTT, and fibrinogen

Urinalysis Panel

- Color, Clarity, pH, Protein, Blood, Ketones, Urobilinogen, Glucose, Leukocyte Esterase, Nitrite, Specific Gravity, Bilirubin, with microscopic analysis in the event there is abnormal Blood, Nitrite, Leukocyte Esterase, or Protein

PD Panel

- TAFIa activity, clot lysis, TAFI antigen, D-dimer