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[redacted]	[redacted]
Print Name	Signature
Vice President, TMCP	08 JAN 2015
Title	Date (DD MMM YYYY)
[redacted]	[redacted]
Print Name	Signature
Executive Director, Biostatistics	08 Jan 2015
Title	Date (DD MMM YYYY)
[redacted]	[redacted]
Print Name	Signature
Vice President, CSPV	08 Jan 2015
Title	Date (DD MMM YYYY)
[redacted]	[redacted]
Print Name	Signature
Vice President, Regulatory Affairs	14 Jan 2015
Title	Date (DD MMM YYYY)
[redacted]	[redacted]
Print Name	Signature
Dicrector, Experimental Medicine	08 Jan 2015
Title	Date (DD MMM YYYY)

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CLINICAL STUDY PROTOCOL

A PHASE 1B/2, MULTI-CENTER, DOUBLE-BLIND (PRINCIPAL INVESTIGATORS AND STUDY SUBJECTS BLINDED, SPONSOR UNBLINDED), PLACEBO-CONTROLLED, RANDOMIZED, SINGLE-ASCENDING DOSE STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF DS-1040B IN SUBJECTS WITH ACUTE ISCHEMIC STROKE

PROTOCOL NUMBER: DS1040-A-U103

IND NUMBER 115473

VERSION 1.0, 29 DECEMBER 2014

DAIICHI SANKYO PHARMA DEVELOPMENT
399 THORNALL STREET
EDISON, NJ 08837

INVESTIGATOR AGREEMENT

A Phase 1b/2, Multi-Center, Double-Blind (Principal Investigators and Study Subjects Blinded, Sponsor Unblinded), Placebo-Controlled, Randomized, Single-Ascending Dose Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of DS-1040b in Subjects with Acute Ischemic Stroke

Sponsor Approval:

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

[redacted] | [redacted]
Print Name | Signature

Director, Experimental Medicine | 08 Jan 2015
Title | Date (DD MMM YYYY)

Investigator's Signature:

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

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

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

<<Insert Name.>> | _____
Print Name | Signature

<<Insert Title.>> | _____
Title | Date (DD MMM YYYY)

PROTOCOL SYNOPSIS

IND Number:	115473
Protocol Number:	DS1040-A-U103
Investigational Product:	DS-1040b
Active Ingredient(s)/INN:	(2*S*)-5-Amino-2-{[1-(*trans*-4-methylcyclohexyl)-1*H*-imidazol-4-yl]methyl}pentanoic acid mono(4-methylbenzenesulfonate)
Study Title:	A Phase 1b/2, Multi-Center, Double-Blind (Principal Investigators and Study Subjects Blinded, Sponsor Unblinded), Placebo-Controlled, Randomized, Single-Ascending Dose Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of DS-1040b in Subjects with Acute Ischemic Stroke
Study Phase:	Phase 1b/2
Indication Under Investigation:	Thrombotic disease (acute ischemic stroke [AIS])
Study Objectives:	The primary objective of the study is to assess the safety and tolerability of DS-1040b (intravenous [IV] infusion over 6 hours) in subjects with AIS within 3 to 8 hours after stroke symptom onset. <u>Secondary Objectives:</u> 1. To assess plasma and urinary pharmacokinetics (PK) of DS-1040b in subjects with AIS. 2. To assess the effect of DS-1040b on fibrinolysis biomarkers in subjects with AIS. 3. To assess the effect of DS-1040b on recanalization at 24 hours in subjects with AIS. 4. To assess the effect of DS-1040b on neurological outcome by using the National Institute of Health Stroke Scale (NIHSS) and functional outcome by using the modified Rankin Scale (mRS) in subjects with AIS.
Study Design:	This is a Phase 1b/2, double-blind (Principal Investigators and study subjects blinded, Sponsor unblinded), placebo-controlled, randomized, single-ascending dose,

	multi-center study to assess the safety, tolerability, PK, and pharmacodynamics (PD) of DS-1040b in subjects with AIS. This study will consist of 5, sequential, ascending-dose cohorts. A total of 64 to 80 subjects with AIS will be enrolled: 8 to 16 subjects each in Cohorts 1 and 2, and 16 subjects each in Cohorts 3, 4 and 5. In each dose cohort, subjects will be randomized to either DS-1040b or placebo in a 3:1 ratio. The assignment to either active drug or placebo will be blinded to the subjects and Principal Investigators. Each subject will receive a single, IV infusion of DS-1040b or placebo. The single, IV infusion will consist of an initial loading dose (25% of the total dose) administered as a 0.5-hour infusion, followed by a maintenance dose (75% of the total dose) administered as a 5.5-hour continuous infusion. Dosing in the successive cohort will occur only after completion of the blinded safety data review (up to discharge) from the previous dose cohort. Upon completion of this blinded safety data review, a dose escalation decision will be made and the dose of the next cohort may be modified (reduced or repeated). Unblinded data will also be used by the Sponsor to perform PK/PD data analysis during the study.
Study Duration:	The study duration is expected to be approximately 15 months. Each randomized subject will receive a single, IV infusion (administered over 6 hours) of DS-1040b or placebo on Day 1. Subjects will remain hospitalized for at least 24 hours after the start of the infusion. After 24 hours, the Principal Investigator may discharge the subject at his/her discretion. Subjects will return to the clinic at Day 30 ± 7 days for follow-up assessments. A follow-up assessment at Day 90 ± 7 days will be conducted by phone.
Study Sites and Location:	Approximately 40 sites in the United States and Europe are planned for this study.
Planned Sample Size:	A total of 64 to 80 subjects with AIS will be enrolled: 8 to 16 subjects each in Cohorts 1 and 2, and 16 subjects each in Cohorts 3, 4, and 5. The sample size of this study is not based on statistical power calculations. The number of subjects at each dose

	level is considered sufficient to achieve the primary objective of the study.
Subject Eligibility Criteria:	Subjects must satisfy all of the following criteria to be included in the study: 1. Subjects have a clinical diagnosis of ischemic stroke with middle cerebral artery (MCA) occlusion (M1 or M2), as demonstrated by computed tomography (CT) angiography or magnetic resonance (MR) angiography. 2. Men and women 18 to 80 years of age, inclusive. 3. Subjects have stroke symptom onset within 3 to 8 hours before initiation of study drug administration. For subjects with a wake-up stroke, symptom onset time refers to the last time the subject was known to be well. 4. Subjects have a NIHSS score > 4 and < 22. 5. Subjects have a body weight of 50 kg to 120 kg, inclusive. 6. Subjects, or their legally authorized representative, must give written informed consent to participate in the study prior to participating in any study-related procedures. A separate written informed consent is required for collecting a blood sample for genotyping. Subjects who meet any of the following criteria will be disqualified from entering the study: 1. Subjects have evidence of intracranial hemorrhage on non-contrast CT (or MR). 2. Subjects have symptoms of subarachnoid hemorrhage, even with normal CT. 3. Subjects have evidence of large MCA territory infarction (sulcal effacement or blurring of gray-white junction in greater than 1/3 of MCA territory). 4. Subjects have prior non-traumatic intracranial hemorrhage. 5. Subjects have known arteriovenous malformation or aneurysm. 6. Subjects have evidence of active bleeding.

7. Subjects have platelet count < 100,000.
8. Subjects have International Normalized Ratio > 1.7.
9. Subjects have used heparin within 48 hours or have an elevated partial thromboplastin time.
10. Subjects have used a nonvitamin K antagonist oral anticoagulant such as dabigatran, rivaroxaban, apixaban, or other factor Xa inhibitors within 48 hours.
11. Subjects have used fondaparinux or low molecular weight heparin at an anticoagulation dose within 48 hours.
12. Subjects with anticipated use of heparin, or fondaparinux or low molecular weight heparin, or nonvitamin K antagonist oral anticoagulant such as dabigatran, rivaroxaban, apixaban, or other factor Xa inhibitors within 48 hours of randomization.
13. Subjects have blood pressure > 185/110 mmHg, or require aggressive medication to maintain blood pressure below this limit (routine medical treatment is allowed to lower the blood pressure below this limit).
14. Subjects have had intracranial surgery, clinically significant head trauma (in the opinion of Principal Investigator), Alteplase treatment, or a previous stroke within 3 months.
15. Subjects have had major surgery within 14 days.
16. Subjects have had gastrointestinal or genitourinary bleeding in the last 21 days.
17. Subjects have had a lumbar puncture (or epidural steroid injection) within 14 days.
18. Subjects have a preexisting disability classified by mRS > 1.
19. Subjects have an estimated glomerular filtration rate (using Modification of Diet in Renal Disease equation) < 60 mL/min/1.73 m^2.
20. Subjects have baseline hemoglobin < 10.5 g/dL.
21. Subjects have a positive pregnancy test. Serum pregnancy tests will be performed in women of childbearing potential (childbearing potential is

	assumed in women up to 55 years of age). 22. Subject is currently participating in another investigational study or has participated in an investigational drug study within 30 days or 5 half-lives of that investigational drug prior to administration of the study drug. 23. Any other reason, in the opinion of the Investigator, which precludes subject participation in the 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. DS-1040b IV solution and placebo will be administered as an initial 0.5-hour infusion (25% of the total dose) followed by a 5.5-hour continuous infusion (75% of the total dose).
Study Endpoints:	**Safety Parameters:** Safety parameters will include serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), physical examination findings, vital sign measurements, standard clinical laboratory parameters (including serum chemistry, hematology, urinalysis, and coagulation parameters), and electrocardiogram (ECG) parameters. Other safety parameters will include bleeding events and neurologic function. Bleeding events will be assessed and categorized as symptomatic intracranial hemorrhage (sICH), any intracranial hemorrhage (ICH), or non-ICH major bleeding. Neurologic function will be measured using the NIHSS. **Pharmacokinetic Parameters:** The PK parameters that will be calculated from the plasma concentrations of DS-1040a using non-compartmental analysis are the area under the concentration-versus-time curve, from time 0 to the last quantifiable concentration sampling point (AUC_{last}), maximum (peak) observed plasma concentration (C_{max}), and time of maximum observed concentration (t_{max}). If data permit, the following parameters will be estimated: the area under the concentration-versus-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$), half-life ($t_{1/2}$), clearance, and the volume of distribution at terminal elimination phase. The PK parameters that will be calculated from urinary

	concentrations of DS-1040a are the amount of drug excreted in urine from 0 to 24 hours (Ae_{0-24}), the renal clearance (CL_R), and the percentage of the dose administered excreted in urine from 0 to 24 hours ($\%Fe_{0-24}$). **Pharmacodynamic Parameters:** Pharmacodynamic analysis for thrombin-activatable fibrinolysis inhibitor (TAFIa) antigen, clot lysis (an exploratory biomarker), D-dimer, and total TAFIa activity will be performed. Remaining blood samples will be used for post-hoc TAFIa inhibition-related coagulation biomarker assessments. Recanalization will be assessed by CT (or MR) angiography at baseline and 24 hours after the start of treatment using Thrombolysis in Myocardial Infarction (TIMI) criteria. **Functional Outcome Parameter:** Functional outcome will be assessed using mRS.
Statistical Analyses:	<u>Safety Parameters:</u> Safety parameters will include SAEs, TEAEs, physical examination findings, vital signs measurements, standard clinical laboratory parameters, 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. Results from placebo-treated subjects will be pooled across cohorts. Bleeding events will be summarized as sICH, any ICH, or non-ICH major bleeding by treatment. Results from placebo-treated subjects will be pooled across cohorts. Neurologic function will be assessed using the NIHSS. Raw values of NIHSS scores will be presented graphically by subject, and will also be summarized by treatment. Change from baseline values will be summarized. Pooled placebo data of all cohorts will be summarized. <u>PK Parameters:</u> 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, including urinary PK 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}, and C_{max}.

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 (C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$) will be examined graphically.

PD Parameters:

Raw values for total TAFIa activity, 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.

Recanalization will be assessed using TIMI reperfusion criteria. Raw values of reperfusion score will be presented graphically by subject, and will also be summarized by treatment. Change from baseline values will be summarized. Data from placebo-treated subjects will be pooled across cohorts.

Functional Outcome Parameters:

Functional outcome will be assessed using the mRS. Raw values of the mRS score will be presented graphically by subject and will also be summarized by treatment. Change from baseline values (inclusion/exclusion criteria) will be summarized. Data from placebo-treated subjects will be pooled across cohorts.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
$\%Fe_{0-24}$	percentage of the dose administered excreted in urine from 0 to 24 hours
Ae_{0-24}	amount of drug excreted in urine from 0 to 24 hours
AIS	acute ischemic stroke
aPTT	activated partial thromboplastin time
AUC	area under the plasma concentration-time curve
AUC_{all}	area under the plasma concentration-time curve from the time of dosing to the time of the last observation
AUC_{last}	area under the concentration-versus-time curve, from time 0 to the last quantifiable concentration sampling point
AUC_{inf} or AUC_{0-inf}	area under the concentration-versus-time curve, from time 0 extrapolated to infinity
%CV	coefficient of variation
C_0	plasma concentration at time 0
C_{24h}	plasma concentration at time 24 hours
$C_{24\ 5h}$	plasma concentration at time 24.5 hours
CFR	Code of Federal Regulation
CL_R	renal clearance
C_{max}	maximum (peak) observed plasma concentration
CRO	contract research organization
CSPV	Clinical Safety and Pharmacovigilance
CT	computed tomography
DSPD	Daiichi Sankyo Pharma Development
EC	ethics committee
ECASS	European Cooperative Acute Stroke Study
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
GCP	Good Clinical Practice
HI	hemorrhagic infarction
ICF	informed consent form
ICH	intracranial hemorrhage
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
IxRS	interactive response system
MCA	middle cerebral artery
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

MR	magnetic resonance
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PGx	pharmacogenomic(s)
PH	parenchymal hemorrhage
PK	pharmacokinetic(s)
PT	prothrombin time
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAVER	serious adverse event report
SD	standard deviation
sICH	symptomatic intracranial hemorrhage
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	half-life
TAFIa	thrombin-activatable fibrinolysis inhibitor
TEAE	treatment-emergent adverse event
TIMI	Thrombolysis in Myocardial Infarction
TK	toxicokinetic
t_{max}	time of maximum observed concentration
US	United States
WHO	World Health Organization

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Data Summary

1.1.1. Investigational Product

1.1.1.1. Name

DS-1040b

Chemical Name: (2*S*)-5-Amino-2-{[1-(*trans*-4-methylcyclohexyl)-1*H*-imidazol-4-yl]methyl}pentanoic acid mono(4-methylbenzenesulfonate)

1.1.1.2. Description

DS-1040b is a tosylate salt of DS-1040a. All doses and concentrations of DS-1040b are based on the content of the free form, DS-1040a.

DS-1040b is an inhibitor of the activated form of thrombin-activatable fibrinolysis inhibitor (TAFIa) antigen intended to be used for the treatment of thrombotic diseases including acute ischemic stroke (AIS).

1.1.1.3. Intended Use Under Investigation

For this Phase 1b/2 study, DS-1040b will be evaluated as a single, intravenous (IV) infusion administered to subjects with AIS. This study will assess the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of DS-1040b.

1.1.1.4. Nonclinical Studies

Nonclinical studies have been undertaken with DS-1040b. Additional information on nonclinical studies is available in the Investigator's Brochure.[1]

In a single-dose toxicity study, rats were given a 30, 100, or 300 mg/kg IV bolus injection (injection volume, 10 mL/kg; injection rate, 1.2 mL/min; and injection duration, approximately 0.9 minutes to 1.3 minutes). All animals given 300 mg/kg died immediately after the bolus injection. No macroscopic findings were observed in any of the dead animals. At 100 mg/kg, transient irregular respiration was observed in all animals immediately after the bolus injection and disappeared within 30 minutes. There were no deaths at 100 mg/kg. In the toxicokinetic (TK) analysis, plasma concentration at time 0 (C_0) and the area under the plasma concentration-time curve from the time of dosing to the time of the last observation (AUC_{all}) values of DS-1040a generally increased with the doses of 30 mg/kg and 100 mg/kg. There were no apparent sex differences in TK parameters.

In a single-dose toxicity study, cynomolgus monkeys were given a 10, 30, 100, 300, or 1000 mg/kg IV bolus injection (injection volume, 4 mL/kg, injection rate; 3 mL/min; and injection duration, approximately 4 minutes to 6 minutes). All animals given 1000 mg/kg died immediately after the bolus injection. No macroscopic findings were observed in the dead animals. At 300 mg/kg, a marked decrease in activity was observed in all

animals and disappeared within 30 minutes. There were no deaths at 300 mg/kg. In the TK analysis, the C_0 and AUC_{all} values of DS-1040a generally increased with the dose, ranging from 10 mg/kg to 300 mg/kg. There were no apparent sex differences in TK parameters.

In a 14-day, repeated-dose, toxicity study of DS-1040b, rats were given 0, 10, 30, or 100 mg/kg IV bolus injections (injection volume, 10 mL/kg; injection rate, 1.2 mL/min; and injection duration, approximately 0.9 minutes to 1.6 minutes). One female, given 100 mg/kg, showed irregular respiration and convulsions and died immediately after the bolus injection on Day 12. No macroscopic findings were observed in the dead animal. The cause of death could not be identified. In surviving animals in the 100 mg/kg group, transient irregular respiration was observed immediately after every dosing in all animals but disappeared within 30 minutes. No treatment-related changes were observed in any of the other examinations at 100 mg/kg. The no observed adverse effect level (NOAEL) was considered to be 30 mg/kg/day for both sexes. In the TK analysis, the mean C_0 and AUC_{all} values of DS-1040a generally increased with dose. There were no apparent changes after repeated dosing or apparent sex differences in the TK parameters.

In a 14-day, repeated-dose, toxicity study of DS-1040b, cynomolgus monkeys were given 0, 10, 30, and 100 mg/kg IV bolus injections (injection volume, 4 mL/kg; injection rate, 3 mL/min; and injection duration, approximately 3 minutes to 5 minutes). No deaths occurred at doses up to 100 mg/kg. Ptosis was observed in 3 of 5 males and females given 100 mg/kg, and 1 female among them showed side position, sitting position, ananastasia, shivering, eyelid closure, irregular respiration, and mouth breathing. All these findings were observed immediately after the bolus injection and disappeared within almost 30 minutes. No treatment related changes were noted in any of the other examinations at doses up to 100 mg/kg. The NOAEL was considered to be 30 mg/kg/day for both sexes. In the TK analysis, the mean C_0 and AUC_{all} values of DS-1040a generally increased with dose. There were no apparent changes after repeated dosing or apparent sex differences in the TK parameters.

In an extended, single-dose, toxicity study, rats were given a 0, 22, 66, or 220 mg/kg continuous IV infusion (0.5 hour short-term infusion followed by 24-hour continuous infusion). The infusion volume and rate of short-term infusion and continuous infusion were set at 4 mL/kg/0.5 h and 40 mL/kg/24 h, respectively. No deaths or test article-related toxicities were observed in any of the groups. The NOAEL was 220 mg/kg for both sexes. In the TK analysis, the mean plasma concentration at 24.5 hours after the initiation of dosing ($C_{24.5h}$) and AUC_{all} values of DS-1040a generally increased with dose. There were no apparent sex differences in the TK parameters.

In an extended, single-dose, toxicity study, cynomolgus monkeys were given 0, 6.6, 22, or 66 mg/kg continuous IV infusion (0.5-hour short-term infusion followed by 24-hour continuous infusion). The infusion volume and rate of short-term infusion and continuous infusion were set at 1.2 mL/kg/0.5 h and 12 mL/kg/24 h, respectively. Neither deaths nor test article-related toxicities were observed in any of the groups. The NOAEL was 66 mg/kg for both sexes. In the TK analysis, the $C_{24.5h}$ and AUC_{all} values of DS-1040a generally increased with dose. There were no apparent sex differences in the TK parameters.

In conclusion, DS-1040b induced acute toxicities at high doses by bolus injection. 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. In the continuous infusion toxicity studies with a 0.5-hour short-term infusion followed by 24-hour continuous infusion of DS-1040b, no significant toxic findings were noted in any examination including clinical observation and histopathology.

1.1.1.5. Clinical Experience

Two clinical studies have completed in humans with DS-1040b.

The first-in-human study (DS1040-A-U101) was a Phase 1, single-blind (study subjects and Investigator blinded, Sponsor unblinded), placebo-controlled, randomized, 3-part, single-ascending dose, single-center 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 healthy subjects were enrolled in this study and 2 dosing regimens were evaluated: a 0.5-hour 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 placebo) 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.

Overall, the DS-1040b doses were well tolerated in young and elderly subjects. All treatment emergent adverse events (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.

The change in coagulation parameters prothrombin time (PT), internal normalized ratio (INR), activated partial thromboplastin time (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.

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 notable safety concerns. 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.

1.2. Study Rationale

DS-1040b is an inhibitor of the activated form of TAFIa intended to be used for the treatment of thrombotic diseases including AIS. This is the first study to assess the safety, PK, and PD of a single, IV dose of DS-1040b in subjects with AIS.

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 2 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.

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

DS-1040b will be administered as a single, IV infusion. It will be administered in doses of 0.6, 1.2, 2.4, 4.8, or 9.6 mg. The single, IV infusion will consist of an initial loading dose (25% of the total dose) administered as a 0.5-hour infusion followed by a maintenance dose (75% of the total dose) administered as a 5.5-hour continuous infusion. See Section 3 for a detailed description of the overall study design.

1.5. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), United States (US) Food and Drug Administration GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56, and 312, as appropriate, and other applicable local regulations.

1.5.1. Subject Confidentiality

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

The Investigator must ensure that the subject's anonymity is maintained. On the electronic Case Report Forms (eCRFs) or other documents submitted to DSPD and/or its contract research organization (CRO) designee, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to DSPD and/or the CRO (eg, signed Informed Consent Forms [ICFs]) should be kept in strict confidence by the Investigator.

In compliance with applicable local guidelines and International Conference on Harmonisation GCP guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of that the regulatory agency(s), and the Ethics Committee (EC) or Institutional Review Board (IRB) direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

1.5.2. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. The written ICF should be prepared in the local language(s) of the potential subject population.

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

The subject's written informed consent should be obtained prior to his/her participation in the study, and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the subject or a

legally acceptable representative, and by the 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 or legal representative. The date and time (if applicable) that informed consent was given should be recorded on the eCRF.

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

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

The consent for pharmacogenomics (PGx) sampling should be documented in the subject's written informed consent. The PGx ICF should be signed and personally dated by the subject or the subject's legal representative prior to his/her participation in the study. Participation in PGx sampling is optional for all subjects. Those subjects who choose not to provide a sample for PGx sampling may still participate in the main portion of the study.

For subjects participating in this study at sites in the US, an additional consent is required for the Health Insurance Portability and Accountability Act.

1.5.3. Regulatory Compliance

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

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

The Investigator must submit and, where necessary, obtain approval from the IRB/EC and/or DSPD for all subsequent protocol amendments and changes to the ICF or changes of the investigational site, facilities, or personnel. The Investigator should notify the IRB/EC of deviations from the protocol or SAEs occurring at the site and other adverse event reports received from DSPD and/or the CRO, in accordance with local procedures.

As required by local regulations, the DSPD local Regulatory Affairs group will insure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to assess the safety and tolerability of DS-1040b (IV infusion over 6 hours) in subjects with AIS within 3 to 8 hours after stroke symptom onset.

2.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To assess the plasma and urinary PK of DS-1040b in subjects with AIS.
- To assess the effect of DS-1040b on fibrinolysis biomarkers in subjects with AIS.
- To assess the effect of DS-1040b on recanalization at 24 hours in subjects with AIS.
- To assess the effect of DS-1040b on neurological outcome by using the National Institute of Health Stroke Scale (NIHSS) and functional outcome by using the modified Rankin Scale (mRS) in subjects with AIS.

2.2. Study Hypothesis

Within the dose range evaluated, DS-1040b will be safe and tolerable in subjects with AIS.

3. STUDY DESIGN

3.1. Overall Plan

3.1.1. Study Type

This is a Phase 1b/2, double-blind (Principal Investigators and study subjects blinded, Sponsor unblinded), placebo-controlled, randomized, single-ascending dose, multi-center study to assess the safety, tolerability, PK, and PD of DS-1040b in subjects with AIS.

3.1.2. Treatment Groups

This study will consist of 5, sequential, ascending-dose cohorts. A total of 64 to 80 subjects with AIS will be enrolled: 8 to 16 subjects each in Cohorts 1 and 2, and 16 subjects each in Cohorts 3, 4, and 5. In each dose cohort, subjects will be randomized to DS-1040b or placebo in a 3:1 ratio. The Principal Investigator and the subject will be blinded to the subject's assignment to either DS-1040b or placebo. Each subject will receive a single, IV infusion of DS-1040b or placebo. The single, IV infusion will consist of an initial loading dose (25% of the total dose) administered as a 0.5-hour infusion, followed by a maintenance dose (75% of the total dose) administered as a 5.5-hour continuous infusion. The planned dose level for each cohort is listed below in Table 3.1.

Table 3.1: Treatment Groups

Cohort	Number of Subjects	DS-1040b Treatment per Subject
1	6 (or 12)[a]	0.6 mg: loading dose of 0.15 mg IV infusion over 0.5 hour, followed by a maintenance dose of 0.45 mg IV infusion over 5.5 hours
	2 (or 4)[a]	Placebo
2	6 (or 12)[a]	1.2 mg: loading dose of 0.3 mg IV infusion over 0.5 hour, followed by a maintenance dose of 0.9 mg IV infusion over 5.5 hours
	2 (or 4)[a]	Placebo
3	12	2.4 mg: loading dose of 0.6 mg IV infusion over 0.5 hour, followed by a maintenance dose of 1.8 mg IV infusion over 5.5 hours
	4	Placebo
4	12	4.8 mg: loading dose of 1.2 mg IV infusion over 0.5 hour, followed by a maintenance dose of 3.6 mg IV infusion over 5.5 hours
	4	Placebo
5	12	9.6 mg: loading dose of 2.4 mg IV infusion over 0.5 hour, followed by a maintenance dose of 7.2 mg IV infusion over 5.5 hours
	4	Placebo

IV = intravenous.
a: Cohort 1 and 2 will start with an initial cohort of 8 subjects (6 active and 2 placebo). An expansion cohort of another 8 subjects (6 active and 2 placebo) may be added during the study.

Dosing in the successive cohort will occur only after completion of the blinded safety data review (up to discharge) from the previous dose cohort. Upon completion of this

blinded safety data review, a dose escalation decision will be made and the dose of the next cohort may be modified (reduced or repeated). Unblinded data will also be used by the Sponsor to perform PK and PD data analysis during the study.

Dose escalation based on symptomatic intracranial hemorrhage (sICH) criteria will be conducted in the following manner:

Cohort 1 will start with 8 subjects (6 active and 2 placebo; Cohort 1a). If no sICH is observed in the 6 active-treated subjects, Cohort 2 will start after the dose escalation safety data review. If 1 instance of sICH is observed in 1 of the 6 active-treated subjects of Cohort 1a, an expansion cohort (Cohort 1b) of 8 subjects (6 active and 2 placebo) will be enrolled and treated at the same dose level as Cohort 1a. If no sICH is observed in Cohort 1b, Cohort 2 will start after the dose escalation data review. If 1 sICH is observed in Cohort 1b, the predefined stopping criteria of sICH (2 out of 12 active-treated subjects) will be considered met and no further dose escalation will occur (refer to Section 3.1.6).

Cohort 2 will be conducted in the same manner as Cohort 1.

In Cohorts 3, 4, and 5, 16 subjects will be enrolled in each cohort. Within each cohort, if sICH is observed in 2 out of 12 active-treated subjects, sICH stopping criteria will be considered met and no further dose escalation will occur. Following an in-depth safety data review, the study may be terminated or continued with a modified (lower) dose.

Additionally, if 4 or more cases of sICH in the active-treated subjects are observed across all completed cohorts at any time during the study, the stopping criteria for sICH will be considered met and no further dose escalation will occur; however, the study may proceed at a lower dose.

Each randomized subject will receive a single, IV infusion (administered over 6 hours) of DS-1040b or placebo on Day 1. Subjects will remain hospitalized for at least 24 hours after the start of the infusion. After 24 hours, the Principal Investigator may discharge the subject at his/her discretion after completing early discharge procedures (Section 6.5). Subjects will return to the clinic on Day 30 ± 7 days for follow-up assessments. A follow-up assessment on Day 90 ± 7 days will be conducted by phone.

For additional details of the study procedures and the Schedule of Events see Section 6 and Section 17.5, respectively.

3.1.3. Study Endpoints

The endpoints for this study include the following:

- Safety parameters:

Serious adverse events, TEAEs, physical examination findings, vital sign measurements, standard clinical laboratory parameters (including serum chemistry, hematology, urinalysis, and coagulation parameters), and electrocardiogram (ECG) parameters.

Other safety parameters will include bleeding events and neurologic function. Bleeding events will be assessed and categorized as sICH, any intracranial hemorrhage (ICH), or non-ICH major bleeding. Neurologic function will be measured using the NIHSS.

- Pharmacokinetic parameters:

Standard noncompartmental PK parameters will be assessed. Plasma samples for PK assessments will be taken at multiple timepoints in the study. Additionally, a PK sample may also be obtained outside of the specified timepoints during the study if deemed clinically necessary. Urine PK samples will also be collected and evaluated in the study.

- Pharmacodynamic parameters:

Pharmacodynamic analysis for TAFIa antigen and clot lysis along with D-dimer and total TAFIa activity will be performed. Remaining blood samples will be used for post-hoc TAFIa inhibition-related coagulation biomarker assessments.

Recanalization will be assessed during the study.

- Other parameters:

An assessment of functional outcome using the mRS will be performed during the study.

3.1.4. Duration of the Study

The study duration is expected to be approximately 15 months.

3.1.5. Duration of Subject Participation

Each randomized subject will receive a single, IV infusion (administered over 6 hours) of DS-1040b or placebo on Day 1. Subjects will remain hospitalized for at least 24 hours after the start of infusion. After 24 hours, the Principal Investigator may discharge the subject at his/her discretion after completing early discharge procedures (Section 6.5). Subjects will return to the clinic on Day 30 ± 7 days for follow-up assessments. A follow-up assessment on Day 90 ± 7 days will be conducted by phone.

3.1.6. Stopping Rules

The following criteria will be used to stop dose escalation during the study:

Symptomatic intracranial hemorrhage within 36 hours following the start of infusion:

- 2 cases of sICH in active-treated subjects per dose level
- 4 cases of sICH in active-treated subjects cumulatively across dose levels

Other major bleeding (non-ICH) during hospitalization and up to 5 days following the start of infusion:

- 2 cases of major bleeding defined as Thrombolysis in Myocardial Infarction (TIMI) in active-treated subjects per dose level

Other:

- In addition, DSPD, the PAREXEL Medical Monitor, and the Investigator may decide to halt dose escalation under other circumstances, such as data indicating organ toxicity, even if it is not covered by any of the prespecified stopping rules.

If any of the above criteria are met within a dose group (or across dose groups for sICH), escalation to a higher dose level will not proceed. Following an in depth review of all safety data available across the study, one of the following recommendations will be made:

- Terminate the study.
- Continue with the study but at a modified dose (eg, a dose between the current dose and the previous lower dose).
- Continue with the study but expand either the current or next cohort by an appropriate number (8 to 16) of subjects for more detailed safety evaluation.

3.2. Selection of Doses

3.2.1. Experimental Treatments

This study will enroll subjects into cohorts as outlined in Section 3.1.2.

In this study, a range of single, IV doses will be evaluated during the dose escalation. The starting dose of 0.6 mg (loading dose of 0.15 mg as 0.5-hour IV infusion, followed by a maintenance dose of 0.45 mg as 5.5-hour IV infusion), was selected based on safety, PK, and PD data from a healthy volunteer (including elderly subjects) study (DS1040-A-U101).

Based on human PK data, the projected maximum (peak) observed concentration in circulating blood (C_{max}) and area under the plasma concentration-time curve (AUC) of the 0.6 mg starting dose in a typical subject with a body weight of 75 kg and a creatinine clearance of 90 mL/min are: 13.2 ng/mL and 118 ng·h/mL, respectively, which are 1.2% and 1.5% of the highest exposure achieved in healthy young subjects (mean C_{max} = 1102 ng/mL in the 12 mg 0.5-hour IV infusion dose level and mean area under the concentration-versus-time curve from time 0 extrapolated to infinity [AUC_{inf}] = 8116 ng·h/mL in the 40 mg 24-hour IV infusion dose level), and 2.6% and 10.4% of the highest exposure achieved in elderly subjects (mean C_{max} = 505 ng/mL and mean AUC_{inf} = 1135 ng·h/mL in the 6 mg 0.5-hour IV infusion dose level). Projected plasma exposure levels for planned doses are summarized in Table 3.2. Based on human biomarker data, the projected PK exposure at the starting dose of 0.6 mg will likely result in an approximately 15% reduction in clot lysis time.

The maximum dose of 9.6 mg (loading dose of 2.4 mg as 0.5-hour IV infusion, followed by maintenance dose of 7.2 mg as 5.5-hour IV infusion) was selected to achieve full effect on clot lysis time reduction. Projected C_{max} and AUC_{inf} are 212 ng/mL and 1889 ng·h/mL, respectively, which are 19% and 23% of the highest exposure achieved in healthy, young subjects, and 42% and 166% of the highest exposure achieved in elderly subjects.

Table 3.2: Projected Plasma Pharmacokinetic Parameters

Cohort	Total Dose (mg)	Loading Dose (mg) over 0.5 hours	Maintenance Dose (mg) over 5.5 hours	Simulated Plasma PK Parameters			
				$C_{0.5h}$ (ng/mL)	C_{6h} (C_{max}) (ng/mL)	t_{max} (h)	AUC (ng·h/mL)
1	0.6	0.15	0.45	11.9	13.2	6	118
2	1.2	0.3	0.9	23.8	26.5	6	236
3	2.4	0.6	1.8	47.7	52.9	6	472
4	4.8	1.2	3.6	95.3	106	6	944
5	9.6	2.4	7.2	191	212	6	1889

AUC = area under the plasma concentration-time curve $C_{0\ 5h}$ = maximum plasma concentration at 0.5 hours; C_{6h} = maximum plasma concentration at 6 hours; PK = pharmacokinetic; t_{max} = time of maximum observed concentration.
Simulation assumptions: body weight = 75 kg, CL_{cr} = 90 mL/min

3.2.2. Control Treatments

The placebo for DS-1040b will be 0.9% Sodium Chloride Injection, USP and will be provided by the site. In order to maintain the blind, placebo (0.9% Sodium Chloride Injection, USP) will be administered in the same manner as DS-1040b in the respective cohorts. The detailed procedures for drug preparation will be provided separately in the pharmacy manual.

4. STUDY POPULATION

The study population will comprise male and female subjects 18 to 80 years of age, inclusive, with a clinical diagnosis of ischemic stroke with middle cerebral artery (MCA) occlusion (M1 or M2), as demonstrated by computed tomography (CT) or magnetic resonance (MR) angiography, who experienced stroke symptom onset within 3 to 8 hours prior to the initiation of study drug administration (for wake-up strokes, symptom onset time refers to last time the subject was known to be well).

4.1. Enrollment

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (initials, age, sex) and the date and outcome of the screening process (eg, enroll in the study, reason for ineligibility, refused to participate).

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

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

Each subject or legally acceptable representative will be provided with information about the study, will have all questions answered to their satisfaction, and will sign and date an ICF. This will be completed before any study-specific procedures are performed. Additional information about informed consent procedures is provided in Section 1.5.2.

4.1.1. Inclusion Criteria

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

1. Subjects have a clinical diagnosis of ischemic stroke MCA occlusion (M1 or M2), as demonstrated by CT or MR angiography.
2. Men and women 18 to 80 years of age, inclusive.
3. Subjects have stroke symptom onset within 3 to 8 hours before initiation of study drug administration. For subjects with a wake-up stroke, symptom onset time refers to the last time the subject was known to be well.
4. Subjects have a NIHSS score > 4 and < 22.
5. Subjects have a body weight of 50 kg to 120 kg, inclusive.
6. Subjects, or their legally authorized representative, must give written informed consent to participate in the study prior to participating in any study-related procedures. A separate written informed consent is required for collecting a blood sample for genotyping.

4.1.2. Exclusion Criteria

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

1. Subjects have evidence of intracranial hemorrhage on noncontrast CT (or MR).
2. Subjects have symptoms of subarachnoid hemorrhage, even with normal CT.
3. Subjects have evidence of large MCA territory infarction (sulcal effacement or blurring of gray-white junction in greater than 1/3 of MCA territory).
4. Subjects have prior non-traumatic intracranial hemorrhage.
5. Subjects have known arteriovenous malformation or aneurysm.
6. Subjects have evidence of active bleeding.
7. Subjects have platelet count < 100,000.
8. Subjects have INR > 1.7.
9. Subjects have used heparin within 48 hours or have an elevated partial thromboplastin time.
10. Subjects have used a nonvitamin K antagonist oral anticoagulant such as dabigatran, rivaroxaban, apixaban, or other factor Xa inhibitors within 48 hours.
11. Subjects have used fondaparinux or low molecular weight heparin at an anticoagulation dose within 48 hours.
12. Subjects with anticipated use of heparin, or fondaparinux or low molecular weight heparin, or nonvitamin K antagonist oral anticoagulant such as dabigatran, rivaroxaban, apixaban, or other factor Xa inhibitors within 48 hours of randomization.
13. Subjects have blood pressure > 185/110 mmHg, or require aggressive medication to maintain blood pressure below this limit (routine medical treatment is allowed to lower the blood pressure below this limit).
14. Subjects have had intracranial surgery, clinically significant head trauma (in the opinion of Principal Investigator), Alteplase treatment, or a previous stroke within 3 months.
15. Subjects have had major surgery within 14 days.
16. Subjects have had gastrointestinal or genitourinary bleeding in the last 21 days.
17. Subjects have had a lumbar puncture (or epidural steroid injection) within 14 days.
18. Subjects have a preexisting disability classified by mRS > 1.
19. Subjects have an estimated glomerular filtration rate (using Modification of Diet in Renal Disease [MDRD] equation) < 60 mL/min/1.73 m^2.
20. Subjects have baseline hemoglobin < 10.5 g/dL.

21. Subjects have a positive pregnancy test. Serum pregnancy tests will be performed in women of childbearing potential (childbearing potential is assumed in women up to 55 years of age).
22. Subject is currently participating in another investigational study or has participated in an investigational drug study within 30 days or 5 half-lives of that investigational drug prior to administration of the study drug.
23. Any other reason, in the opinion of the Investigator, which precludes subject participation in the study.

4.2. Removal of Subjects From Therapy

4.2.1. Reasons for Withdrawal/Early Discontinuation

Any subject who discontinues from study treatment for any reason will have their study treatment discontinuation recorded.

Subjects may be withdrawn from the study after signing informed consent for the following reasons:

- Adverse event
- Lost to follow up
- Death
- Protocol violation
- Withdrawal of consent by subject
- Study terminated by Sponsor
- Other (eg, discretion of the Investigator)

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

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures (Section 4.2.2).

4.2.2. Withdrawal Procedures

Protocol-specified withdrawal procedures are the same as those performed at the Day 5 visit (Section 6.5).

4.2.3. Subject Replacement

Any subject who discontinues study participation before completing all study visits will not be replaced.

4.2.4. Subject Re-screening Procedures

Not applicable.

5. TREATMENTS ADMINISTERED

5.1. Investigational Products

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

DS-1040b Injection 10 mg/10 mL is transferred into IV infusion solution (0.9% Sodium Chloride Injection, USP), as shown in Table 5.1. The placebo for DS-1040b will be 0.9% Sodium Chloride Injection, USP. In order to maintain the blind, placebo solution will be administered in the same manner as the DS-1040b IV solution in the respective cohort. The detailed procedures for drug preparation will be provided separately in pharmacy manual.

DS-1040b IV solution will be administered as an initial 0.5-hour infusion (25% of the total dose) followed by a 5.5-hour continuous IV infusion (75% of the total dose). In each cohort, 8 to 16 subjects will be randomized in a ratio of 3:1 (active:placebo). The assignment of either active or placebo will be blinded to subjects, Investigators, and the CRO staff.

5.1.1. Method of Assigning Subjects to Treatments and 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, and CRO staff.

Allocation of treatment by subject at the clinical site will be done by contacting the interactive response system (IxRS).

- In the case of an emergency where, in the opinion of the Investigator, discontinuation of study treatment is not sufficient and the study treatment must be unblinded in order to evaluate further course of action, the Investigator must make every effort to contact the PAREXEL Medical Monitor prior to unblinding a subject. In the rare event that contact with the PAREXEL Medical Monitor is not possible prior to unblinding, the Investigator reserves the right to unblind in a true emergency, where subject safety is at immediate risk. All sites will be provided with details on how to contact the IxRS for unblinding at the start of the study, and this process will be documented in the IxRS manual.
- Upon unblinding, the Investigator will complete the Emergency Unblinding by Investigator Form and will return it to Daiichi Sankyo Medical Monitor.
- If the emergency unblinding is needed as the result of an SAE, the SAE must be immediately reported, as defined in the protocol (Section 9.3).

5.1.2. Method of Assessing Treatment Compliance

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.

5.1.3. Labeling and Packaging

DS-1040b Injection 10 mg/10 mL is 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.

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

5.1.4. 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.

Table 5.1: Treatment Preparation

Drug Level	Drug Product (solution in glass vial)	Active Treatment		Loading Dose (0.5-hour infusion, infusion rate: 0.83 mL/min)	Maintenance Dose (5.5-hour infusion, infusion rate: 0.23 mL/min)	Placebo (0.9% Sodium Chloride Injection, USP)
		Drug Product Solution Volume	Additional 0.9% Sodium Chloride Injection, USP Volume			
0.6 mg	10 mg/10 mL	0.6 mL	99.4 mL	0.15 mg in 25 mL	0.45 mg in 75 mL	100 mL
1.2 mg	10 mg/10 mL	1.2 mL	98.8 mL	0.30 mg in 25 mL	0.90 mg in 75 mL	100 mL
2.4 mg	10 mg/10 mL	2.4 mL	97.6 mL	0.60 mg in 25 mL	1.8 mg in 75 mL	100 mL
4.8 mg	10 mg/10 mL	4.8 mL	95.2 mL	1.2 mg in 25 mL	3.6 mg in 75 mL	100 mL
9.6 mg	10 mg/10 mL	9.6 mL	90.4 mL	2.4 mg in 25 mL	7.2 mg in 75 mL	100 mL

5.1.5. Storage

Drug supplies must be stored in a secure, limited access storage area under the recommended 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 consult the Sponsor to determine whether the Investigational Product can be used.

5.1.6. 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. The Receipt of Shipment Form should be faxed as instructed on the form. The original will be retained at the site. In addition, the Investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

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

At the end of the study, or as directed, all 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.

5.1.7. Retention Samples

There will be no retention sample taken during this study.

5.2. Concomitant Medications

For the specified number of days prior to enrollment and through study completion or upon early withdrawal, the following medications are not allowed:

Prior to enrollment (Day 1):

- Heparin use within 48 hours or elevated partial thromboplastin time.

- Nonvitamin K antagonist oral anticoagulant use within 48 hours such as dabigatran, rivaroxaban, apixaban, or other factor Xa inhibitors.
- Fondaparinux or low molecular weight heparin use within 48 hours at an anticoagulation dose.

Within 24 hours postdose period:

- Antiplatelet agents (aspirin, clopidogrel). After 24 hours post dose, use of antiplatelet agent will be at the discretion of the Principal Investigator.

Within 48 hours postdose period:

- Heparin, nonvitamin K antagonist oral anticoagulant such as dabigatran, rivaroxaban, apixaban, or other factor Xa inhibitors.

During the study, concomitant medications required to treat TEAEs will be permitted. Other concomitant medications for preexisting 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.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Section 17.5. Unless otherwise specified, all postdose timepoints are after the start of investigational product administration.

6.1. Day 1

6.1.1. Predose

The following assessments will be performed predose:

- Obtain written (ie, signed and dated) informed consent
- Assess inclusion/exclusion criteria
- Record medical history information (including mRS, if possible)
- Record prior/concomitant medication
- Obtain a blood sample for follicle stimulating hormone evaluation
- Obtain a serum sample for pregnancy testing in women of childbearing potential (childbearing potential is assumed in women up to 55 years of age)
- Perform a complete physical examination including weight (can be estimated by the subject, family members, or the Principal Investigator)
- Perform a non-contrast CT or MR, followed by angiography (after hemorrhagic stroke is ruled out)
- Administer the NIHSS
- Obtain supine vital sign measurements
- Perform a 12-lead ECG in triplicate
- Obtain blood samples for safety laboratory assessments (serum chemistry and hematology) (Section 9.5)
- Obtain a urine sample for urinalysis (Section 9.5)
- Obtain blood samples for PT, INR, aPTT, and fibrinogen (Section 9.5)
- Obtain PD blood sample (TAFIa activity, clot lysis, TAFI antigen, D-dimer) (Section 8.2)
- Assess subjects for adverse events
- Obtain PK blood sample

6.1.2. 0 Hour

The following assessments will be performed at 0 hour:

- Administer DS-1040b
- Start collection of urine for PK assessments

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

6.1.3. 0.5 Hours Postdose

The following assessments will be performed 0.5 hours after dosing started:

- Obtain supine vital sign measurements
- Perform a 12-lead ECG in triplicate
- Obtain blood samples for PT, INR, aPTT, and fibrinogen (Section 9.5)
- Obtain PD blood sample (TAFIa activity, clot lysis, D-dimer) (Section 8.2)
- Obtain PK blood sample

6.1.4. 3 Hours Postdose

The following assessments will be performed 3 hours after dosing:

- Obtain supine vital sign measurements
- Perform a 12-lead ECG in triplicate
- Obtain PK blood sample

6.1.5. 6 Hours Postdose

The following assessments will be performed 6 hours after dosing:

- Obtain supine vital sign measurements
- Perform a 12-lead ECG in triplicate
- Obtain blood samples for PT, INR, aPTT, and fibrinogen (Section 9.5)
- Obtain PD blood sample (TAFIa activity, clot lysis, TAFI antigen, D-dimer) (Section 8.2)
- Administer the NIHSS
- Assess subjects for adverse events
- Obtain PK blood sample

6.1.6. 9 Hours Postdose

The following assessment will be performed 9 hours after dosing:

- Obtain PK blood sample

6.1.7. 12 Hours Postdose

The following assessments will be performed 12 hours after dosing:

- Obtain supine vital sign measurements
- Perform a 12-lead ECG in triplicate
- Obtain blood samples for PT, INR, aPTT, and fibrinogen (Section 9.5)
- Obtain PD blood sample (TAFIa activity, clot lysis, D-dimer) (Section 8.2)
- Obtain PK blood sample

6.2. Day 2

The following assessments will be performed on Day 2 (24 hours after dosing):

- Obtain supine vital sign measurements
- Record prior/concomitant medication
- Perform a 12-lead ECG in triplicate
- Obtain blood samples for safety laboratory assessments (serum chemistry and hematology) (Section 9.5)
- Obtain a urine sample for urinalysis (Section 9.5)
- Obtain blood samples for PT, INR, aPTT, and fibrinogen (Section 9.5)
- Obtain PD blood sample (TAFIa activity, clot lysis, TAFI antigen, D-dimer) (Section 8.2)
- Perform a CT or MR angiography
- Administer the NIHSS
- Assess subjects for adverse events
- Obtain PK blood sample

Collection of urine for urine PK should stop 24 hours after dosing.

Subjects can be discharged at any time after 24 hours following dosing, at the discretion of the Principal Investigator. In the case of discharge prior to Day 5, after completing early discharge procedures (described in Section 6.5), no further assessments are required until the Day 30 Follow-up Visit.

6.3. Day 3

The following assessments will be performed on Day 3 (48 hours after dosing):

- Obtain supine vital sign measurements
- Record prior/concomitant medication
- Obtain blood samples for safety laboratory assessments (serum chemistry and hematology) (Section 9.5)

- Obtain a urine sample for urinalysis (Section 9.5)
- Obtain blood samples for PT, INR, aPTT, and fibrinogen (Section 9.5)
- Obtain PD blood sample (TAFIa activity, clot lysis, D-dimer) (Section 8.2)
- Assess subjects for adverse events
- Obtain PK blood sample

6.4. Day 4

The following activities and/or assessments will be performed on Day 4 (72 hours after dosing):

- Record prior/concomitant medication
- Assess subjects for adverse events
- Obtain PK blood sample

6.5. Day 5 (Early Discharge or Discontinuation)

The following activities and/or assessments will be performed on Day 5 (96 hours after dosing):

- Perform a complete physical examination
- Record prior/concomitant medication
- Administer the NIHSS
- Administer the mRS
- Assess subjects for adverse events
- Obtain PK blood sample

Attempts should be made to complete all assessments during this visit for subjects who withdraw from the study. After discharge, no further assessments are required until the Day 30 Follow-up Visit.

6.6. Follow-up

6.6.1. Day 30

The following activities and/or assessments will be performed on Day 30 ± 7 days:

- Perform a complete physical examination
- Administer the NIHSS
- Administer the mRS
- Assess subjects for adverse events

6.6.2. Day 90

The following activities and/or assessments will be performed on Day 90 ± 7 days:

- Administer the mRS
- Assess subjects for adverse events

This visit will occur as a phone contact.

6.7. Protocol Deviations

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

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 investigational treatment, and had at least one administration of investigational product, data should be collected for safety purposes.

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

7. EFFICACY ASSESSMENTS

Efficacy will not be evaluated in this study.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

Blood and urine samples for PK/PD analyses will be obtained at the timepoints specified in the Schedule of Events (Section 17.5). Additionally, PK samples may be modified or deleted at any time during the study based on the dose escalation data review. Instructions for the handling of blood samples and shipping of plasma samples for PK/PD analyses are included in a separate document (eg, 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.

Bioanalysis of DS-1040a will be performed using a validated method based on liquid chromatography coupled with tandem mass spectrometry which will be covered in a separate document prepared by the bioanalytical laboratory.

8.1. Pharmacokinetic (PK) Variable(s)

Blood samples for PK assessment will be collected predose and 0.5, 3, 6, 9, 12, 24, 48, 72, and 96 hours postdose. The PK parameters that will be calculated from the plasma concentrations of DS-1040a using noncompartmental analysis are shown in Table 8.1.

Table 8.1: Pharmacokinetic Parameters - Plasma

Parameter	Definition
AUC_{last} (ng·h/mL)	The area under the concentration-versus-time curve, from time 0 to the last quantifiable concentration sampling point
C_{max} (ng/mL)	Maximum (peak) observed plasma concentration
t_{max} (h)	The time of maximum observed concentration

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-inf}), $t_{1/2}$, clearance, and the volume of distribution in the terminal elimination phase.

Urine collection for PK assessment will start following dosing and stop at 24 hours postdose. The PK parameters that will be calculated from the urine concentration of DS-1040b are shown in Table 8.2.

Table 8.2: Pharmacokinetic Parameters - Urine

Parameter	Definition
Ae_{0-24}	Cumulative amount of compound excreted into urine up to 24 hours
CL_R	Renal clearance
$\%Fe_{0-24}$	Cumulative percentage of dose excreted into urine up to 24 hours

8.2. Pharmacodynamic (PD) Variable(s)

Blood samples for PD assessment will be collected predose and 0.5, 6, 12, 24, and 48 hours postdose.

Pharmacodynamic analysis for TAFI antigen, clot lysis (an exploratory biomarker), D-dimer, and total TAFIa activity 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.

A CT or MR angiography will be performed to assess MCA recanalization. The same imaging method (CT or MR) will be used in the all assessments for an individual subject. Additional imaging assessments can be performed at the discretion of the Investigator. An external reviewer (a neuroradiologist), who is blinded to the treatment assignments, will review all CT or MR scans to assess recanalization by use of the TIMI reperfusion criteria:

- Score 0: no perfusion
- Score 1: perfusion past the initial occlusion, but no distal branch filing
- Score 2: perfusion with incomplete or slow distal branch filing
- Score 3: full perfusion with filing of all distal branches, including M3, M4

8.3. Biomarker and Exploratory Variable(s)

As part of this study, a single 4 mL blood sample will also be collected for PGx analysis. DNA biomarkers will be examined to evaluate the correlations between TAFI-related genes and response to the study drug, and/or the therapeutic response to the disease condition (eg, stroke). In addition, the correlation between TAFI-related genes and disease condition (eg, stroke) will be explored. All participants should be presented with the PGx ICF at screening. 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.

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 ASSESSMENTS

9.1. Adverse Events

All clinical adverse events occurring after the subject signs the ICF and up to 90 days after the single dose of study medication, whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event eCRF 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 SAEs are to be reported according to the procedures in Section 9.3 SAE Reporting-Procedure for Investigators. Always report diagnosis as the adverse event or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the adverse event 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 adverse event or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an adverse event or SAE, but the reason for the procedure may be an adverse event or SAE. Preplanned (prior to signing the ICF) procedures or treatments requiring hospitalization for preexisting conditions which do not worsen in severity should not be reported as SAEs (see Section 9.2 for Definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

At each visit, the Investigator will determine whether any adverse events 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 adverse events to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. 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 as an adverse event on the eCRF, and if serious, report as an SAE following the procedures in Section 9.3.

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 up until resolution or until they become clinically not relevant.

9.2. Definitions

9.2.1. Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event 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 (International Conference on Harmonisation 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.

9.2.2. Serious Adverse Event

Any untoward medical occurrence that at any dose:

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

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

- A procedure is not an adverse event or SAE, but the reason for the procedure may be an adverse event or SAE.
- Preplanned (prior to signing the ICF) procedures or treatment requiring hospitalizations for preexisting conditions which do not worsen in severity are not SAEs.

9.2.3. Adverse Event Severity

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.

9.2.4. Causality Assessment

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

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

9.2.5. Action Taken Regarding the Study Product

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

9.2.6. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The subject fully recovered from the adverse event with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the adverse event are still present and observable.
  - Include sequelae/residual effects.

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

9.2.7. Other Action Taken for Event

- 1 = None.
  - No treatment was required.
- 2 = Medication required.
  - Prescription and/or over-the-counter medication was required to treat the adverse event.
- 3 = Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the adverse event, whether or not medication was required.
- 4 = Other.

9.3. Serious Adverse Event Reporting–Procedure For Investigators

9.3.1. Initial Reports

All AEs and SAEs will be reported in the CRF/eCRF. All SAEs must be reported on a Daiichi Sankyo 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 the 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. Source documents will be retained in the site's files 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 nonurgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

See Section 15.2.3 for contact information for SAE reporting. Please call the local SAE Hotline (see Study Manual) or your study monitor for any questions on SAE reporting.

9.3.2. Notifying Regulatory Authorities, Investigators, IRB/EC, and Competent Authorities

Daiichi Sankyo and/or CRO will inform Investigators, IRBs/ECs, and regulatory authorities of any Suspected Unexpected Serious Adverse Event Reactions (SUSARs)

occurring in other study centers or other Daiichi Sankyo studies of the investigational product, as appropriate per local reporting requirements.

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

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

9.4. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or up to the last safety follow-up visit (90 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. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, postpartum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.3.

9.5. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

- Hematology variables, including but not limited to red blood cell count, hemoglobin, hematocrit, platelet count, and white blood cell count with 5-part differential, including absolute neutrophil count
- Serum chemistry variables, including but not limited to calcium, glucose, serum creatinine, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, sodium, potassium, bicarbonate, and chloride
- Urinalysis variables, including but not limited to protein, glucose, blood, microscopy assessments, and specific gravity
- Coagulation: INR, PT, aPTT, and fibrinogen
- Serum pregnancy test (for women of childbearing potential)

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 clinically significant.

9.6. Vital Signs

Vital sign measurements will include systolic blood pressure, diastolic blood pressure, and heart rate. All measurements will be taken in a supine position.

9.7. 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.

9.8. Physical Findings

A complete physical examination, with the exception of the genitourinary system and prostate, will be performed on each subject at baseline prior to dosing, at discharge, 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 prior to enrollment for qualification.

9.9. Other Safety Assessments

9.9.1. Bleeding

Bleeding will be assessed and categorized as sICH, any ICH, or non-ICH major bleeding (as defined by TIMI criteria). All bleeding events will be assessed by the Principal Investigator. In addition, any ICH event will be centrally assessed by 2 external blinded reviewers (1 neuroradiologist and 1 neurologist). This review is independent of the Principal Investigator's assessment.

All sICH events will be classified according to clinical and CT criteria. Hemorrhagic infarction 1 (HI1) is defined as small petechiae along the margins of the infarct; hemorrhagic infarction 2 (HI2) is defined as confluent petechiae within the infarcted area but no space-occupying effect; parenchymal hemorrhage (PH1) is defined as blood clots in 30% or less of the infarcted area with some slight space-occupying effect; and parenchymal hemorrhage (PH2) is defined as blood clots in more than 30% of the infarcted area with substantial space-occupying effect. Symptomatic intracranial hemorrhage is defined as (European Cooperative Acute Stroke Study [ECASS] criteria[2]) blood at any site in the brain on the CT scan (as centrally assessed by the external blinded reviewers, independent of the assessment by the Investigator), documentation by the Investigator of clinical deterioration, or adverse events indicating clinical worsening (eg, drowsiness, increase of hemiparesis) or causing a decrease in the NIHSS score of 4 or more points, and intracranial hemorrhage is determined as the predominant cause of clinical deterioration.

Non-ICH major bleeding is defined as (TIMI hemorrhage criteria) clinically significant overt signs of hemorrhage associated with a drop in hemoglobin of > 5 g/dL (or, when hemoglobin is not available, an absolute drop in hematocrit of > 15%).

9.9.2. Neurologic Function

Neurologic function will be measured using the NIHSS.

10. OTHER ASSESSMENTS

Functional outcome will be assessed using mRS.

11. STATISTICAL METHODS

Detailed statistical methods will be described in a Statistical Analysis Plan or data analysis plan. The analysis plan will be finalized prior to database lock.

11.1. Analysis Sets

The following analysis sets will be used during this study:

The randomized analysis set will include all subjects who signed (or signed by their legally acceptable representative) the ICF and were randomized into the study.

The safety analysis set will include all subjects who received at least 1 dose of investigational product.

The PK analysis set will include all subjects who received a dose of DS-1040b and have sufficient plasma concentration data for DS-1040a to characterize the PK parameters.

The PD analysis set will include all subjects who received a dose of study medication and have at least 1 postdose PD assessment.

11.2. General Statistical Considerations

The primary analysis is to assess the safety and tolerability of DS-1040b in subjects with AIS.

In all the analyses, data will be tabulated with descriptive summary statistics for exploratory and hypothesis-generating purpose. No imputation will be performed for dropouts or missing data.

All quantitative 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 the coefficient of variation (%CV) for geometric mean will also be calculated for $AUC_{0\text{-}inf}$, AUC_{last}, and C_{max}. Frequency counts and percentages will be provided for categorical data. Summaries will be provided for each active dose arm and on the pooled placebo arm. When data are available for both predose and postdose assessments, summaries will be provided on predose assessments, postdose assessments, and change from predose to postdose assessments, respectively.

Results from placebo-treated subjects will be pooled across cohorts

11.3. Study Population Data

Demographic characteristics will be summarized for the randomized analysis set and presented according to the treatment to which they were randomized. The number of subjects who complete the study will be presented. The timing and primary reason for withdrawal will be summarized. Inclusion of subjects in each of the defined analysis sets will also be summarized. Continuous demographic variables for all subjects will be summarized with descriptive statistics. Categorical demographic variables will be

summarized with frequency counts and corresponding percentages. Pooled placebo data of all cohorts will be summarized.

11.4. Efficacy Analyses

Not applicable.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

11.5.1. Pharmacokinetic Analyses

Descriptive statistics (sample size [N], number missing [N missing], arithmetic mean, SD, %CV, minimum, maximum, and median)of DS-1040a plasma concentrations at each sampling time point and all PK parameters, including urinary PK will be presented by dose. In addition, the geometric mean and %CV for geometric mean will also be calculated for the PK parameters $AUC_{0\text{-}inf}$, AUC_{last}, and C_{max}.

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 at each timepoint and mean and median graphs.

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

11.5.2. Pharmacodynamic Analyses

Raw values for total TAFIa activity, clot lysis time, 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.

Recanalization will be assessed using TIMI reperfusion criteria. Raw values of reperfusion score will be presented graphically by subject, and will also be summarized by treatment. Change from baseline values will be summarized. The shift (baseline to posttreatment) of the number and percentage of subjects in TIMI reperfusion criteria will be tabulated by treatment. Pooled placebo data of all cohorts will be summarized.

11.5.3. Biomarker and Exploratory Analyses

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

11.6. Safety Analyses

Safety parameters will include SAE, TEAEs, physical examination findings, vital signs measurements, standard clinical laboratory parameters (serum chemistry, hematology, urinalysis, and coagulation parameters), 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. Results from placebo-treated subjects will be pooled across cohorts.

11.6.1. Adverse Event Analyses

Results from placebo subjects will be pooled across cohorts.

A TEAE is defined as an adverse event that: emerges during the treatment period (from first dose date until 30 days after the last dosing date), having been absent at predose; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment relative to the predose state, when the adverse event is continuous.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized and listed by treatment, System Organ Class (SOC), and preferred term.

The number and percentage of subjects reporting TEAEs will be tabulated by SOC and preferred term.

Similarly, the number and percentage of subjects reporting treatment emergent SAEs will be tabulated, as well as TEAEs/SAEs considered related to DS-1040b.

A by subject adverse event (including TEAEs) data listing including, but not limited to, verbatim term, preferred term, SOC, and relationship to study drug will be provided.

Deaths, other SAEs, and other significant adverse events, including those leading to permanent discontinuation from DS-1040b, will be listed.

11.6.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics by treatment will be provided for the clinical laboratory test results (hematology, serum chemistry, urinalysis, and coagulation) and changes from baseline by scheduled time of evaluation. Percentage change from baseline will also be summarized for coagulation variables. Clinical laboratory values will be summarized by treatment and listed with abnormal values flagged.

Abnormal laboratory results will be evaluated. A shift table (in categories of low, normal and high, when appropriate) will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance will be listed.

Data for PT, INR, and aPTT will be summarized with descriptive statistics by treatment.

11.6.3. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation. Vital signs will be summarized by treatment and listed with abnormal values flagged.

11.6.4. Electrocardiogram Analyses

Electrocardiogram parameters (PR, RR, QRS, QT, corrected QT interval using Bazett's formula [QTcB], and corrected QT intervals using Fridericia's formula [QTcF]) will be summarized by treatment using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation. The corrected QT intervals using Bazett's and Fridericia's formula will be calculated as follows: QTcB = QT/(RR)^1/2 and QTcF = QT/(RR)^1/3.

The incidence of notable ECG changes in maximum absolute QT, QTcF and QTcB intervals (> 450, > 480, and > 500 ms) over all postdose evaluations, as well as in QT, QTcF and QTcB maximum changes from baseline (> 30 and > 60 ms) over all postdose evaluations will be summarized. A listing of ECG data will be provided.

Electrocardiogram values will be summarized by treatment and listed with abnormal values flagged.

11.6.5. Physical Finding Analyses

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

11.6.6. Other Safety Analyses

11.6.6.1. Bleeding

Bleeding events will be summarized as the following categories: sICH, any ICH, or non-ICH major bleeding. The number and percentage of subjects experiencing these bleeding events will be tabulated by treatment. Results from placebo-treated subjects will be pooled across cohorts.

11.6.6.2. Neurologic function

Neurologic function will be assessed using the NIHSS. Raw values of the NIHSS score will be presented graphically by subject, and will also be summarized by treatment. Change from baseline values will be summarized. The number and percentage of subjects of 0 or 1 point of postdose NIHSS and 4 points or more improvement of NIHSS will be tabulated by scheduled time of evaluation and treatment. Pooled placebo data of all cohorts will be summarized.

11.7. Other Analyses

Functional outcome will be assessed using the mRS. Raw values of mRS scores will be presented graphically by subject, and will also be summarized by treatment. Change from baseline values (inclusion/exclusion criteria) will be summarized. The number and percentage of subjects of 0 or 1 point of postdose mRS will be tabulated by scheduled time of evaluation and treatment. Pooled placebo data of all cohorts will be summarized.

11.8. Interim Analyses

No formal interim analysis is planned.

11.9. Data and Safety Monitoring Board

Two external reviewers (1 neurologist and 1 neuroradiologist), who are not involved in the study conduct and are blinded to the treatment assignments, will assess all cases of ICH. The neuroradiologist will review all CT or MR scans (independent to the Investigator at site), and classify any ICH findings according to the ECASS morphologic definitions.

The neurologist will assess whether neurologic deterioration is due to ICH, or other causes.

Dose Escalation Safety Data Review:

Blinded clinical (bleeding and other AEs) and safety laboratory data of each completed dose level will be reviewed prior to escalation to the next dose level. The dose escalation decision will be made based on this data review. Participants in the dose escalation safety data review meetings are the following: Clinical Study Leader, Medical Monitors from the Sponsor and PAREXEL, external reviewers for ICH, Clinical Study Manager, and Statistician from the Sponsor.

11.10. Sample Size Determination

The sample size for this study is not based on statistical power calculations. The number of subjects at each dose level is considered sufficient to achieve the primary objective of this study.

At least 8 subjects each will be enrolled in the first 2 cohorts. An additional expansion cohort of 8 subjects may be added during the first 2 cohorts if additional information is needed in order to move forward with the last 3 cohorts. At least 16 subjects each will be enrolled in the last 3 cohorts: 12 of which will be randomized to active treatment, and 4 to placebo treatment. A stopping rule of sICH is predefined: 2 cases of sICH in 12 active-treated subjects per dose level, or 4 cases of sICH in active-treated subjects cumulatively across dose levels. This sample size and stopping rule are determined in consideration of sICH observation and dose escalation criteria in small dose cohort safety studies conducted with tissue plasminogen activator.[3,4] The incidence of sICH observed is about 16% per dose level in these studies. The sample size and stopping rule of sICH in current study are designed to prevent a greater incidence of sICH than observed with tissue plasminogen activator in small dose cohort safety studies.

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/EC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1. Monitoring and Inspections

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

The monitor is responsible for visiting site(s) at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to International Conference on Harmonisation GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

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

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

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

12.2. Data Collection

The eCRF completion should be kept current to enable the monitor to review the subject's status throughout the course of the study. The eCRF will be completed, reviewed, and signed off or e-signed by the Investigator.

The Investigator e-signs the eCRF according to the study data flow.

Any data recorded on the study eCRF will be collected and included in the database according to CDISC standards and subjected to the same procedures as other data.

12.3. Data Management

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

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications given to DSPD and/or the CRO. Data will be vetted both electronically and manually 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. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the Clinical/Data Management review process, queries will be raised and 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 adverse events and medical history will be coded using MedDRA. Concomitant medications will be coded using the current 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 eCRFs will be included on the Signature List.

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

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

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

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

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.

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.

12.5. Record Keeping

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

13. FINANCING AND INSURANCE

13.1. Finances

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

13.2. Reimbursement, Indemnity, and Insurance

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

14. PUBLICATION POLICY

15. STUDY ADMINISTRATIVE INFORMATION

15.1. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/EC, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/EC within five working days. The Sponsor will assure the timely submission of amendments to regulatory authorities.

15.2. Address List

15.2.1. Sponsor

Daiichi Sankyo Pharma Development
399 Thornall Street
Edison, NJ 08837
Phone: (732) 590-5000
Fax: (732) 906-5690

15.2.1.1. Sponsor Medical Monitor

[redacted]
Senior Director, Experimental Medicine
Daiichi Sankyo Pharma Development
[redacted]

15.2.1.2. Sponsor Clinical Study Leader

[redacted]
Director, Experimental Medicine
Daiichi Sankyo Pharma Development
[redacted]

15.2.1.3. Sponsor Clinical Operations Delivery Lead or Clinical Study Manager

Sponsor Clinical Operations Delivery Lead

[redacted]
Director, Clinical Development Operations
Daiichi Sankyo Pharma Development
[redacted]

Sponsor Clinical Operations Delivery Executive

[redacted]
Senior Clinical Study Manager
Translation Medicine Clinical Pharmacology
Daiichi Sankyo, Inc.
[redacted]

15.2.2. CRO

PAREXEL International Corporation
195 West Street
Waltham, MA 02451
Phone: (781) 487 9900

15.2.2.1. CRO Medical Monitor

[redacted]
Senior Medical Director
PAREXEL International Corporation
195 West Street
Waltham, MA 02451
[redacted]

15.2.2.2. CRO Project Manager

PAREXEL International Corporation
195 West Street
Waltham, MA 02451
[redacted]

15.2.3. Drug Safety

15.2.3.1. Sponsor: DSPD Serious Adverse Event Reporting Form General Contact

[redacted]

15.2.3.2. CRO

PAREXEL International Corporation
195 West Street
Waltham, MA 02451
[redacted]

15.2.4. Data Management

[redacted]
Senior Project Data Manager
EU Biostatistics & Data Operations
Daiichi Sankyo Development Ltd.
[redacted]

15.2.5. Biological Specimens (Plasma and Urine PK Samples)

[redacted]
Project Director
Worldwide Clinical Trials
8609 Cross Park Drive
Austin, Texas 78754
[redacted]

[redacted]
Sample Control
Worldwide Clinical Trials
8609 Cross Park Drive
Austin, Texas 78754
[redacted]

15.2.6. Interactive Response System (IxRS)

TBD

15.2.7. Genomics Laboratory

[redacted]
ILS Genomics, LLC
100 Perimeter Park, Suite C
Morrisville, NC 27560
[redacted]

15.2.8. Biological Pharmacodynamic Specimens for PT, INR, aPTT, D-dimer, and Total TAFIa Activity

[redacted]
Project Coordinator
Medpace Reference Laboratories USA
5375 Medpace Way
Cincinnati, Ohio 45227
[redacted]

15.2.9. Biological Pharmacodynamic Specimens for TAFI Antigen

[redacted]
Project Manager/Principal Investigator
Intertek Pharmaceutical Services
3985 Sorrento Valley Blvd. Suite C
San Diego, CA 92121 USA
[redacted]

15.2.10. Biological Pharmacodynamic Specimens for Clot Lysis

TBD

16. REFERENCES

[1] Investigator's Brochure for DS-1040b. Daiichi Sankyo Pharma Development. Version 2.0, 26 Jun 2013.
[2] Hacke W, Kaste M, Fieschi C, et al. Randomised, double-blind, placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). Lancet 1998;352:1245-51.
[3] Brott T, Haley E, Levy D, et al. Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 1992;23:632-40.
[4] Haley E, Levy D, Brott T, et al. Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered 91-180 minutes from onset. Stroke 1992;23:641-5.

17. APPENDICES

17.1. Additional Information on Investigational Products

Not applicable.

17.2. Instructions for Specimen Collection, Storage and Shipment

17.2.1. Sample Handling Instructions for Pharmacogenomic Samples

The detail instructions for collection, storage, handling, and shipping of blood samples for pharmacogenomics samples will be provided separately in a laboratory manual.

17.2.2. Collection, Storage, Handling, and Shipping of Blood Samples for PD Analysis

The detail instructions for collection, storage, handling, and shipping of blood samples for PD analysis will be provided separately in a laboratory manual.

17.2.3. Collection, Storage, Handling ,and Shipping for Sample Analysis of Plasma DS-1040b

The detail instructions for collection, storage, handling, and shipping of blood samples for PK analysis will be provided separately in a laboratory manual.

17.2.4. Collection, Storage, Handling, and Shipping for Sample Analysis of Urinary DS-1040b

The detail instructions for collection, storage, handling, and shipping of urine samples for PK analysis will be provided separately in a laboratory manual.

17.3. Listing of Laboratory Assays

The total blood volume that will be taken from each subject is 176.7 mL.

Test	Volume per test (mL)	Number of Timepoints per Subject	Total Volume (mL)
Baseline			
Serum chemistry, follicle stimulating hormone, serum pregnancy	8.5	1	8.5
Hematology	4	1	4
PT/INR/aPTT/fibrinogen	2.7	1	2.7
Other visits:			
Genotyping (optional)	4	1	4
Serum chemistry (including PT/INR/fibrinogen when scheduled at the same time)	8.5	4	34
Hematology	4	4	16
PT/INR/aPTT/fibrinogen/D-dimer (Local laboratory)	2.7	3	8.1
PT/INR/aPTT (Central laboratory – Medpace, Inc.)	2.7	6	16.2
D-dimer (Central laboratory – Medpace)	2.7	6	16.2
Total TAFIa activity (Central laboratory)	2.7	6	16.2
Clot lysis (Central laboratory)	2.7	6	16.2
TAFI antigen (Central laboratory)	2.7	3	8.1
PK	2	9	18
Total			**168.2**

aPTT = activated partial thromboplastin time; HIV = human immunodeficiency virus; INR = International Normalized Ratio; PK = pharmacokinetic; PT = prothrombin time; TAFIa = thrombin-activatable fibrinolysis inhibitor.

17.4. Substudies

Not applicable.

17.5. Schedule of Events

	Treatment Period											Follow-Up Period[a]	
Day	1							2	3	4	5[b]	30	90
Hour	Predose	0	0.5	3	6	9	12	24	48	72	96		
Informed consent	X												
Inclusion/exclusion criteria	X												
Medical history	X												
Prior and concomitant medication	X							X	X	X	X		
Follicle stimulating hormones (women only)	X												
Serum pregnancy test	X												
Genotyping sample			----------X[c]----------										
Weight	X												
Physical examination	X										X	X	
Vital signs (supine)	X		X	X	X		X	X	X				
Electrocardiogram (12-lead in triplicate)	X		X	X	X		X	X					
Serum chemistry	X							X	X				
Hematology	X							X	X				
Urinalysis	X							X	X				
PT, INR, aPTT, fibrinogen	X		X		X		X	X	X				
TAFIa activity, clot lysis	X		X		X		X	X	X				
TAFI antigen	X				X			X					
D-dimer	X		X		X		X	X	X				
MR/CT angiography	X							X					
NIHSS	X				X			X			X	X	
mRS											X	X	X
Adverse event monitoring	----------X[d]----------												
Drug administration		X											
PK plasma sample	X		X	X	X	X	X	X	X	X	X		
Start urine collection		X											
Stop urine collection								X					
Check-in	X												
Check-out											X		
Study confinement	----------X----------												

aPTT = activated partial thromboplastin time; CT = computed tomography; HIV = human immunodeficiency virus; INR = International Normalized Ratio; PT = prothrombin time; MR = magnetic resonance; mRS = Modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale; PK = pharmacokinetic; TAFIa = thrombin-activatable fibrinolysis inhibitor.

a: Follow-up at 30 day ± 7 days will be conducted in an outpatient setting. Follow up at 90 days ± 7 days will be conducted by phone.

b: Discharge, early discharge, or discontiuation. Subjects will be hospitalized for at least 24 hours following the start of infusion. After 24 hours, it is at the Principal Investigator's discretion when to discharge the subject. These procedures will be completed before discharge, early discharge, or discontinuation.
c: May be performed at any timepoint postdose.
d: Continuous.