CLINICAL STUDY PROTOCOL

A Phase 1 Clinical Study of DS-1040b-A Study to Evaluate the Safety of DS-1040b in Patients with Acute Ischemic Stroke in Whom a Thrombectomy Device is Indicated (A Randomized, Single-blind, Placebo-controlled, Study)-
(DS1040-A-J110)

VERSION 03.01.000, 17 Apr 2019

DAIICHI SANKYO CO., LTD.

INVESTIGATOR AGREEMENT

A Phase 1 Clinical Study of DS-1040b –A Study to Evaluate the Safety of DS-1040b in Patients with Acute Ischemic Stroke in Whom a Thrombectomy Device is Indicated (A Single-blind, Placebo-controlled, Randomized Study)– (DS1040-A-J110)

Sponsor Approval:

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

PPD
Print Name

Signature

PPD Clinical Development Department, R&D Division
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 Harmonization guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

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

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

Print Name

Signature

Title

Date (DD MMM YYYY)

PROTOCOL SYNOPSIS

Protocol Number:	DS1040-A-J110
Investigational Product:	DS-1040b
Active Ingredient(s)/INN:	To be determined.
Study Title:	A phase 1, multicenter, randomized, single-blind, placebo-controlled, single-ascending dose study to assess the safety, pharmacokinetics, and pharmacodynamics of DS-1040b in acute ischemic stroke subjects with thrombectomy.
Study Phase:	Phase 1
Indication Under Investigation:	Acute ischemic stroke
Study Objectives:	Primary objectives: To confirm the safety and tolerability of DS-1040b in patients with acute ischemic stroke in whom thrombectomy device treatment is indicated. The primary endpoints are the incidences of symptomatic and asymptomatic intracranial hemorrhage and non-intracranial (Thrombolysis in Myocardial Infarction [TIMI]) major bleeding. Secondary objectives: 1. To measure plasma and urine drug concentrations and calculate pharmacokinetic parameters 2. To examine the effect of DS-1040b on fibrinolytic biomarkers (activated form of thrombin-activatable fibrinolysis inhibitor [TAFIa] activity, D-dimer level, and thrombin-activatable fibrinolysis inhibitor [TAFI] antigen level) 3. To assess the change in the National Institutes of Health Stroke Scale (NIHSS) score at 24 hours after the start of study drug administration relative to baseline and the proportion of subjects with good prognosis (modified Rankin Scale [mRS] score of 0 to 2) on Days 30 and 90 Type of study objectives: Safety/tolerability
Study Design:	Type of study: Intervention Type of intervention: Drug Type of indication: Treatment Study design: Parallel-cohort (a parallel-cohort ascending dose design) Level of blindness: Single-blind Type of comparator: Placebo Treatment groups: Five groups (DS-1040b 0.6 mg, 1.2 mg, 2.4 mg, 4.8 mg, and placebo groups) Randomization: Not applicable. Stratification factors: Not applicable. Allocation ratio: Only a DS-1040b group in the 0.6 mg cohort; and a ratio of DS-1040b: placebo = 3:1 per cohort for the 1.2 mg and higher dose cohorts Duration of assessment of each subject: 90 days

	Addition to standard treatment: Applicable Standard treatment indicated: A stent-type thrombectomy device (stent retriever)
Study Duration:	01 Apr 2017 to 30 Jun 2020 Duration of study for each subject: 90 days Duration of study drug administration for each subject: 6 hours
Study Centers and Location:	20 centers in Japan
Subject Eligibility Criteria:	Target disease: Acute ischemic stroke Inclusion Criteria Subjects must satisfy all of the following criteria at the time of informed consent to be included in the study: 1) Male or female aged 20 to < 90 years 2) Having acute ischemic stroke with intracranial artery (internal carotid artery [ICA] or middle cerebral artery [MCA] M1 region) occlusion confirmed by computed tomography angiography or magnetic resonance angiography 3) Thrombectomy can be performed in principle within 8 hours after the onset of ischemic stroke. 4) Receiving treatment with a stent-type thrombectomy device as the initial treatment 5) Having an NIHSS score of >= 6 and Alberta Stroke Program Early CT Score (ASPECTS) of >= 6 Exclusion Criteria Subjects who meet any of the following criteria will be disqualified from entering the study: 1) Having received or planned to receive treatment with a thrombolytic drug 2) Having intracranial or subarachnoid hemorrhage confirmed by head imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) 3) Having experienced a suspected bleeding event, such as gastrointestinal hemorrhage 4) Having a history of intracranial hemorrhage or a cerebral hemorrhage risk such as intracranial tumor, cerebral aneurysm, and cerebral arteriovenous malformation 5) Having a complication of aortic dissection 6) Having a history of serious head/spinal cord injury or surgery within 3 months 7) Having a history of gastrointestinal or urinary tract hemorrhage within 21 days 8) Having undergone major surgery or experienced serious non-head injury within 14 days 9) Having activated partial thromboplastin time (aPTT)

or partial thromboplastin time (PTT) of > 2 times the normal value

10) Having an international normalized ratio (INR) of > 1.7
11) Having a platelet count of < 100,000/mm^3
12) Having uncontrolled hypertension despite drug therapy (systolic > 185 mmHg and diastolic > 110 mmHg)
13) Having a baseline blood glucose level of > 400 mg/dL
14) Having occlusion of at least two major arteries
15) Treatment with a stent-type thrombectomy device is not indicated due to the presence of carotid artery dissection, occlusion/vasculitis of the entire carotid artery/neck, contrast media allergy, etc.
16) Having a severe hepatic disorder (fulminant hepatitis, hepatic cirrhosis, hepatic tumor, or other hepatic disorders meeting any of the following criteria)

Parameter	Criterion
Total bilirubin	>= 3.0 mg/dL
AST (GOT)	>= 2.5 × the upper limit of reference range or >= 100 U/L
ALT (GPT)	>= 2.5 × the upper limit of reference range or >= 100 U/L
ALP	>= 2.5 × the upper limit of reference range

17) Being on chronic dialysis or having a severe renal disorder (eg, nephrotic syndrome, acute/chronic renal failure, uremia, and hydronephrosis) or a serum creatinine level of >= 2 mg/dL
18) Having a history of ischemic stroke within 30 days prior to the study drug administration
19) Having received another study drug in another clinical study within 30 days prior to the study drug administration in this study
20) Being pregnant, having the potential of being pregnant, being breastfeeding, or planning to become pregnant (or having a partner who is planning to become pregnant) while participating in the study
21) Otherwise considered inappropriate for the study by the investigator or subinvestigator

Dosage Form, Dose and Route of Administration:	This study is an intergroup ascending dose study using a total of 4 cohorts. Four doses (0.6, 1.2, 2.4, and 4.8 mg) of DS-1040b will be used. The study drug will be administered intravenously over 6 hours. The 0.6 mg cohort will consist only of a DS-1040b group, to which 6 subjects (or 12 subjects) will be randomized. For other

	dose cohorts, subjects will be randomized to the DS-1040b or placebo group in a 3:1 ratio. Details of the dosing regimen are provided below: The required amount for injection will be removed from the vial and added to 100 mL of 0.9% saline. One-fourth (25%) of the entire amount will be administered intravenously over 30 minutes as a loading dose, followed by a 5.5-hour continuous intravenous infusion of the remaining injection (75%) as a maintenance dose. Administration of a loading dose will in principle be started before recanalization of the occluded vessel is achieved with a thrombectomy device; however, it may be started after the recanalization procedure if it is likely to be achieved prior to study drug administration.
Study Endpoints:	Primary endpoints ✓ Incidence of symptomatic intracranial hemorrhage (defined by the European Cooperative Acute Stroke Study [ECASS]) ✓ Incidence of asymptomatic intracranial hemorrhage ✓ Incidence of non-intracranial (TIMI) major bleeding Secondary endpoints ✓ Blood and urine pharmacokinetics ✓ Fibrinolytic biomarkers (TAFIa activity, D-dimer level, and TAFI antigen level) ✓ Change in the NIHSS score at 24 hours after the start of study drug administration relative to baseline ✓ Proportion of subjects with good prognosis based on the mRS score (mRS score of 0 to 2) on Day 90
Planned Sample Size:	54 subjects (or 60 subjects) (6 or 12 subjects in the 0.6 mg cohort and 16 subjects per cohort in other dose cohorts [a total of 4 cohorts])
Statistical Analyses:	The analytical objective of this study is to confirm the safety and tolerability of DS-1040b in patients with acute ischemic stroke. With regard to the safety, the point estimate and 95% confidence interval will be estimated for the incidences of symptomatic and asymptomatic intracranial hemorrhage events within 24 hours to 36 hours after the start of study drug administration and the incidence of non-intracranial (TIMI) major bleeding within 96 hours after the start of study drug administration. Data from the placebo groups in each cohort will be integrated and data from the DS-1040b groups will be summarized by dose. Adaptive design: Not applicable.

Study Discontinuation Criteria	If the following criterion is met, the study will not proceed to the next cohort and will be discontinued at that point: ✓ Occurrence of two events of symptomatic intracranial hemorrhage (as defined by ECASS)* not attributable to external factors at 36 hours after the start of DS-1040b administration in the DS-1040b group in one cohort If any of the following criteria are met, the necessary actions to be taken to ensure the safety of subjects, including not proceeding to the next cohort, will be considered: ✓ Occurrence of one event of symptomatic intracranial hemorrhage (as defined by ECASS)* not attributable to external factors at 96 hours after the start of study drug administration in the DS-1040b group in one cohort ✓ Occurrence of one event of non-intracranial (TIMI) major bleeding* at 96 hours after the start of study drug administration in the DS-1040b group in one cohort ✓ Occurrence of any event requiring the consideration of study discontinuation, such as a severe organ disorder or treatment-related serious adverse event (SAE) *The final assessment of symptomatic intracranial hemorrhage and (TIMI) major bleeding will be performed by the central adjudication committee member in a blinded fashion. For events meeting any of the following criteria, the sponsor will discuss the matter with the medical expert as appropriate to decide whether or not the study should be discontinued: • New information on the safety of the study drug or information on SAEs • A major violation of Good Clinical Practice (GCP) or the clinical study protocol by either the sponsor, study center, or investigator • Combined elevations of aminotransferase and bilirubin meeting the laboratory criteria for a potential case of Hy's Law • Any other new information obtained during the study

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ABBREVIATION	DEFINITION
ALP	alkaline phosphatase
ALT (GPT)	-alanine aminotransferase (glutamic pyruvic acid transaminase)
AHA	American Heart Association
aPTT	activated partial thromboplastin time
ASA	American Stroke Association
ASPECTS	Alberta Stroke Program Early CT Score
AST (GOT)	-aspartate aminotransferase (glutamic oxaloacetic acid transaminase)
AUC	area under the plasma concentration-time curve
AUCinf	area under the plasma concentration-time curve up to infinity
AUClast	area under the plasma concentration-time curve up to the last quantifiable time
BUN	blood urea nitrogen
C_0	initial plasma concentration
CK (CPK)	creatine kinase (creatine phosphokinase)
CL	total body clearance
CLcr	creatinine clearance
CLr	renal clearance
Cmax	maximum plasma concentration
CRO	contract research organization
CRP	C-reactive protein
CT	computed tomography
CYP	cytochrome P450
DAPT	dual antiplatelet therapy
DS-1040a	the free form of DS-1040b
EC	ethics committee
EC_{50}	50% effective concentration
ECASS	European Cooperative Acute Stroke Study
ECmax	maximum effective concentration
EDC	electronic data capture
FAS	full analysis set
GCP	Good Clinical Practice
γ-GT	gamma-glutamyltransferase-
IC90	90% inhibitory concentration
ICA	internal carotid artery
ICF	informed consent form
ICH	international conference on harmonization
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
LDH	lactic acid (lactate) dehydrogenase
MCA	middle cerebral artery
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
PT	prothrombin time
PTT	partial thromboplastin time
rt-PA	recombinant tissue plasminogen activator

ABBREVIATION	DEFINITION
SHR	spontaneously hypertensive rat
TAFI	thrombin-activatable fibrinolysis inhibitor
TAFIa	activated form of thrombin-activatable fibrinolysis inhibitor
TEAE	Treatment-emergent Adverse Event
TICI	Thrombolysis in Cerebral Infarction
TIMI	Thrombolysis in Myocardial Infarction
Vss	volume of distribution at steady state

1. INTRODUCTION

1.1 Background

Ischemic stroke is a serious disease. Although the exact incidence is unknown, it is estimated to be 100 to 200 per 100,000 persons in Japan, and the risk increases in individuals aged 40 years and older, in whom the estimated incidence is around 600 per 100,000 individuals.[1] In Japan, the number of patients who died of ischemic stroke in 2015 is 64,523, which accounts for approximately 5% of the overall number of deaths.[2]

Currently, two treatments are acknowledged as standard treatment for acute ischemic stroke: a recombinant tissue plasminogen activator (rt-PAs) as a fibrinolysis activator, and a thrombectomy device. However, issues concerning the use of rt-PAs have been pointed out, including limitations on their use to patients within 4.5 hours[3] after the onset of ischemic stroke, and a rate of recanalization of the occluded vessel being approximately 40% in patients with distal MCA occlusion and only <= 10% in patients with ICA occlusion.[4] With thrombectomy devices, on the other hand, although the rate of recanalization of the occluded vessel has improved substantially, and the rate was 82.8% in the SWIFT-PRIME study, in which the therapeutic effect of Solitaire FR, a stent-type thrombectomy device, was investigated in 196 patients with acute ischemic stroke, but the proportion of patients with prognostic improvement (mRS score of 0 to 2) on Day 90 was still 60.2%, indicating divergence between the rates of recanalization and prognostic improvement.[5]

The NASA registry study of Solitaire FR conducted in North America to examine the relationship between reperfusion assessment based on the Thrombolysis in Cerebral Infarction (TICI) grade after device placement and neurological symptom assessment based on the mRS score on Day 90 showed a greater neurological symptom improvement in patients achieving complete reperfusion (TICI 3) compared with patients achieving perfusion in half or more of the target vascular territory (TICI 2b). Treatment with a stent-type thrombectomy device has resulted in an improved therapeutic effect on acute ischemic stroke, but there is still room for improvement, including an increase in the proportion of patients who achieve complete reperfusion.

1.2 Rationale for the Study

1.2.1 Description of the Investigational Drug

DS-1040b is a low molecular weight compound specifically inhibiting TAFIa, an enzyme that suppresses the fibrinolytic system. The production of plasmin required for the activation of fibrinolysis usually occurs on solid-phase fibrin due to the high affinity of fibrinolytic factor plasminogen and plasminogen activator for the fibrin C-terminal lysine residue. Plasminogen activator bound to the C-terminal lysine residue shows 600

times the efficiency of the liquid phase to produce plasmin,[6] and plasmin bound to the C-terminal lysine residue is known to be hardly inhibited by α2-plasmin inhibitors and plasminogen activator inhibitors[7]. TAFIa breaks the C-terminal lysine residue, which in turn decreases the efficiency of plasmin production and the activity of the fibrinolytic system.[8] It is expected that the TAFIa inhibitory effect of DS-1040b will maintain high endogenous efficiency of plasmin production and promote the fibrinolytic response.

It is known that the existing fibrinolysis activator rt-PAs not only dissolve fibrin thrombus but also damage the vascular wall because the activators themselves have protease activity and act systemically. DS-1040b, on the other hand, utilizes only endogenous fibrinolytic factors to specifically promote the efficiency of the plasmin production pathway on the solid-phase fibrin, and thus is likely to have a lower bleeding risk than existing fibrinolysis activators.

1.2.1.1 Non-clinical Pharmacology

The effect of intravenous DS-1040b on the fibrinolytic activity was investigated in a tissue factor-induced rat venous thromboembolism model. Tissue factor solution was administered to male Wistar rats (n = 6 or 7/group) as a continuous intravenous infusion via the jugular vein at 7.5 mL/kg/h for 20 minutes to induce thrombus formation. DS-1040b was intravenously administered by bolus injection (1.0 mL/kg) via the jugular vein at a dose of 0, 0.016, 0.031, 0.063, 0.13, 0.25, or 0.50 mg/kg immediately before tissue factor treatment. Blood was collected at 45 minutes after the start of tissue factor solution to determine the level of plasma D-dimer, an indicator of fibrinolysis, and calculate the 50% effective concentration (EC_{50}) and maximum effective concentration (ECmax). DS-1040b increased the plasma D-dimer levels in a dose-dependent manner ($P < 0.01$ in hypothesis testing using Spearman's rank-correlation coefficient). The EC_{50} and ECmax were 35.8 and 64.7 ng/mL, respectively.

The effect of DS-1040b on cerebral blood flow was evaluated in a rat thromboembolic stroke model. Non-autologous whole blood clots were injected into the ICA of male SHR/Izm rats (n = 9/group) to induce thromboembolic stroke. At 5 minutes after blood clot injection, saline or DS-1040b (3.0 mg/kg) was intravenously administered. Cerebral blood flow of the right MCA was monitored with laser Doppler flowmetry for 110 minutes after blood clot injection. Intravenous DS-1040b (3.0 mg/kg) improved the cerebral blood flow in the rat thromboembolic stroke model.

The effect of DS-1040b on the bleeding time was investigated in a rat model of tail bleeding. Male Wistar rats (n = 9/group) were treated with DS-1040b (3, 10, and 30 mg/kg) or rt-PA (5.2 mg/kg). The rat tail was cut with a razor at 5 minutes after the start of administration, and the bleeding time was evaluated. As a result, rt-PA

significantly prolonged the bleeding time, whereas none of the DS-1040b doses resulted in bleeding time prolongation.

The hemorrhagic risk of DS-1040b was evaluated in a rat cerebral ischemia/reperfusion model. Cerebral ischemia was induced by right MCA occlusion using an intraluminal filament in male SHR/Izm rats (n = 7 to 9/group). At 135 minutes after MCA occlusion, saline or DS-1040b (30 mg/kg) was intravenously administered. As a comparator, rt-PA (7.0 mg/kg) was intravenously administered 175 minutes after MCA occlusion. At 180 minutes after MCA occlusion, the MCA blood flow was reopened. After 60 minutes, the concentration of hemoglobin leaking outside the blood vessel was quantified. As a result, rt-PA significantly promoted hemoglobin leakage, whereas none of the DS-1040b doses resulted in an increase in hemoglobin leakage.

Thus, non-clinical pharmacology studies showed that the risks of hemorrhage and cerebral hemorrhage were low in rat models of tail bleeding and cerebral ischemia/reperfusion at higher doses of DS-1040b than that associated with recanalization of the occluded vessel observed in the rat thromboembolic stroke model (3.0 mg/kg), indicating a low hemorrhagic induction with DS-1040b in these animal models.

1.2.1.2 Pharmacodynamic Drug Interaction

The hemorrhagic risk of DS-1040b when coadministered with edoxaban was evaluated in a rat model of tail bleeding. Male Wistar rats (n = 10/group) were orally treated with edoxaban (10 mg/kg), followed by intravenous administration of DS-1040b (30 mg/kg) or saline. The coadministration of edoxaban and DS-1040b did not affect the bleeding time, compared with edoxaban alone. It was shown that DS-1040b does not increase the prolongation of bleeding time associated with edoxaban.

1.2.1.3 Pharmacokinetics and Drug Metabolism

The pharmacokinetic properties of the free form of DS-1040 (DS-1040a) were investigated in cynomolgus monkeys and rats after intravenous administration. After a single intravenous administration of DS-1040b, the area under the plasma concentration-time curve to infinity (AUCinf) and the initial plasma concentration (C_0) increased dose-dependently. The total body clearance (CL) and the volume of distribution at the steady state (Vss) were approximately constant at doses ranging from 0.1 mg/kg to 1 mg/kg.

The tissue distribution of radioactivity was examined by quantitative whole-body autoradioluminography after a single intravenous administration of ^{14}C-labeled DS-1040a in rats. After intravenous administration, higher radioactivity concentrations in the tissues than those in the blood were detected in the liver, spleen, pituitary, bone marrow,

stomach, thyroid, lung, and small intestine at 5 minutes after administration. The radioactivity concentrations in all tissues decreased time-dependently, though the radioactivity concentrations in the liver, pituitary, and kidney at 24 hours after administration were higher than those in other tissues. The radioactivity concentrations in the cerebrum and cerebellum were lower than those in other tissues at all specimen collection time points. No accumulation was observed in tissues containing melanin, such as the eyeball and skin. The in vitro plasma protein binding ranged from 22.6% to 24.6% in rats, 41.4% to 43.0% in monkeys, and 52.8% to 54.6% in humans. The in vitro blood cell distribution ratio of DS-1040a (0.05, 0.5, and 5 μg/mL) in rat, monkey, and human blood was determined using ^{14}C-labeled DS-1040b. The blood cell distribution of DS-1040a was low in all species (ie blood cell distribution ratio < 11.5%).

Metabolites in rat and monkey plasma obtained after intravenous administration of ^{14}C-labeled DS-1040b were analyzed. On radio high-performance liquid chromatography, DS-1040a was detected as the major peak and metabolites were detected at low levels in the plasma specimens of both species.

After intravenous administration of ^{14}C-labeled DS-1040a to monkeys, 84% of the radioactivity was excreted in the urine. Overall, more than 90% of the dose was recovered in the urine and feces up to 168 hours after intravenous administration. After intravenous administration of ^{14}C-labeled DS-1040b to rats, 79% of the radioactivity was excreted in the urine. Overall, more than 90% of the dose was recovered in the urine and feces up to 168 hours after intravenous administration. In bile duct-cannulated rats, 11% of the radioactivity was excreted into the bile up to 48 hours after an intravenous administration of ^{14}C-labeled DS-1040b.

DS-1040a did not show an inhibitory effect on cytochrome P450 (CYP) isoforms. The IC_{50} values of CYP isoforms were higher than 100 μM. DS-1040a at 100 μM did not show a time-dependent inhibitory effect on CYP isoforms. DS-1040a did not induce mRNA levels and enzymatic activity of CYP3A4, 1A2 and 2B6 in human hepatocytes. In vitro interaction studies of DS-1040a with human uptake and efflux transporters, the IC_{50} values of these transporters were higher than 100 μM.

1.2.1.4 Safety Pharmacology

After intravenous administration of DS-1040b, a transient increase in heart rate and QTc prolongation were observed in monkeys, and central nervous system suppressive effect and irregular respiration in rats. These effects were observed immediately after bolus injection of 100 mg/kg, and resolved within 30 minutes or 2 hours after administration. Oral administration of DS-1040b in a safety pharmacology study showed no effects on the cardiovascular, central nervous, or respiratory system in monkeys at

doses up to 1000 mg/kg.

1.2.1.5 Toxicology

General toxicity studies (a single or 14-day repeated intravenous bolus injection toxicity, extended single 24.5-hour continuous infusion toxicity, 4-day continuous infusion toxicity, and 14- and 28-day repeated oral dose toxicity studies), genotoxicity studies, and hemolysis tests have been conducted in rats and monkeys to date. In addition, local irritation potential at the injection site was evaluated in general toxicity studies.

In the general toxicity studies, acute toxicity (abnormal clinical signs and death) was observed after intravenous bolus injection of DS-1040b at 100 mg/kg or higher in rats and monkeys, without abnormalities indicating organ toxicity. Based on the acute onset and early disappearance of clinical signs, acute toxicities were considered to have occurred only at high concentration exposure by bolus injection.

In 4-day continuous infusion toxicity studies, no toxicological findings were noted in rats; however, mild adrenal hypertrophy without necrotic or degenerative lesions was observed in monkeys at 60 mg/kg/day.

In the 28-day repeated oral dose toxicity studies, thickening of mucosal epithelium in the cecum was observed in male rats at 1000 mg/kg. In monkeys, digit bleeding and histopathological findings of thinning of the stratum corneum with parakeratosis of the digits (on the surface of the palms) were noted at 300 mg/kg or higher, and liquid stools, bleeding from the anus, anus ulceration, and abnormal skin findings (edema, ulceration, and wetness) of the digits, palms, and soles at 1000 mg/kg. The no observed adverse effect level was determined to be 300 mg/kg/day and 100 mg/kg/day for rats and monkeys, respectively. All of the above findings observed in the oral dose toxicity studies showed reversibility in a 28-day recovery period.

DS-1040b showed no genotoxicity, local irritation, or hemolysis.

1.2.1.6 Clinical Studies

A single ascending dose study (DS1040-A-U101) in healthy subjects was conducted in the United States. In Part A (64 subjects), non-elderly subjects received a 0.5-hour intravenous infusion of DS-1040b at doses of 0.1, 0.2, 0.4, 0.8, 1.6, 3, 6, and 12 mg. In Part B (15 subjects), elderly subjects received a 0.5-hour intravenous infusion of DS-1040b at doses of 3 mg and 6 mg. In Part C (24 subjects), non-elderly subjects received a 24-hour intravenous infusion of DS-1040b at doses of 10, 20, and 40 mg. In part A, the plasma concentration of DS-1040a rapidly reached the peak concentration with a median time to reach the maximum plasma concentration (Tmax) of 0.5 hours to 0.67 hours.

Plasma exposure parameters, as measured by Cmax, area under the plasma concentration versus time curve from 0 hours to the last quantifiable concentration (AUClast), and AUCinf, increased with increasing DS-1040b dose at 0.1 mg to 12 mg. In the dose range between 3 mg to 12 mg, the mean CL was consistent (5.44 L/h to 6.24 L/h) and the mean $T_{1/2}$ ranged from 16.46 hours to 22.32 hours. In the dose range between 3 mg to 12 mg, the mean percentage of the DS-1040b dose recovered in urine ranged from approximately 62% to 78% and the mean CL ranged from 3.29 L/h to 4.69 L/h. In part B, Cmax, AUClast, and AUCinf increased with increasing DS-1040b dose over the dose range of 3 mg to 6 mg. In comparison to non-elderly subjects, overall DS-1040a plasma exposure was higher in elderly subjects at the same dose level (3 and 6 mg DS-1040b). The mean CL was slightly lower in elderly subjects compared with non-elderly subjects: 4.06 L/h to 5.37 L/h in the elderly subjects vs 6.04 L/h to 6.24 L/h in non-elderly subjects. The mean $T_{1/2}$ was longer (33.86 hours to 40.68 hours) in elderly subjects than non-elderly subjects (16.50 hours to 16.82 hours) at the same dose level. The mean percentage of the DS-1040b dose recovered in urine was approximately 69% and the mean renal CL ranged from 2.67 L/h to 3.78 L/h. These renal CL values are slightly lower than those observed in healthy non-elderly subjects (4.56 L/h to 4.69 L/h) at the same dose level, which resulted in a longer $T_{1/2}$ in elderly subjects. In part C, plasma DS-1040a concentrations reached an initial peak at 0.5 hours and constant concentrations were achieved by approximately 4 hours and were maintained until the end of the 24-hour infusion. The mean exposure parameters Cmax, AUClast, and AUCinf increased with increasing DS-1040b dose at doses ranging from 10 mg to 40 mg. Mean CL ranged from 4.97 L/h to 5.79 L/h, and mean $T_{1/2}$ ranged from 36.89 hours to 40.67 hours. The mean percentage of the DS-1040b dose recovered in urine was similar across the dose range of 10 mg to 40 mg, at approximately 79% to 80%. The mean renal CL ranged from 4.02 L/h to 4.56 L/h.

In a drug-drug interaction study with aspirin (DS1040-A-E102) conducted in the United Kingdom, the safety and tolerability of DS-1040b given as a single intravenous dose after 5 days of oral aspirin treatment in healthy non-Japanese subjects were evaluated. Each subject received a loading dose of 300 mg aspirin in the morning of Day 1 followed by a daily dose of 75 mg aspirin on Days 2 to 5. In the morning of Day 5, the daily dose of aspirin was followed immediately by a 0.5-hour intravenous infusion of DS-1040b 6 mg. Prolongation of the mean bleeding time (Surgicutt method) was observed throughout the duration of aspirin treatment from baseline to Day 4. Plasma DS-1040a concentration parameters after coadministration of DS-1040b and aspirin were 582 ng/mL and 1118 h·ng/mL for Cmax and AUC, respectively, and no prolongation of the mean bleeding time was observed. A single intravenous dose of DS-1040b after 5

days of aspirin treatment was safe and well-tolerated, and no treatment-related adverse events (AEs) or safety concerns were detected.

In a drug-drug interaction study with enoxaparin (DS1040-A-U104) conducted in the United States, the safety and tolerability of coadministration of enoxaparin (a single subcutaneous injection of 1 mg/kg) and DS-1040b (a 12-hour intravenous infusion of 20 mg) in 24 healthy (non-Japanese) subjects were investigated. Plasma concentrations and pharmacokinetic parameters of DS-1040a were similar to those observed when DS-1040b was administered alone or in combination with enoxaparin. Tolerability and safety were also confirmed.

In a drug-drug interaction study with clopidogrel (DS1040-A-E106) conducted in the United Kingdom, the safety and tolerability of DS-1040b given as a single intravenous dose after 6 days of clopidogrel treatment in 22 healthy (non-Japanese) subjects were evaluated. Each subject received a loading dose of 300 mg clopidogrel in the morning of Day 1, followed by a daily dose of 75 mg clopidogrel on Days 2 to 6. In the morning of Day 6, the daily dose of clopidogrel was followed immediately by a 12-hour intravenous infusion of DS-1040b 20 mg. Compared with pretreatment baseline, prolongation of the mean bleeding time (Surgicutt method) was observed with clopidogrel given until Day 5. Plasma DS-1040a concentration parameters after coadministration of DS-1040b and clopidogrel were 290 ng/mL and 3670 h·ng/mL for Cmax and AUC, respectively, and no prolongation of the mean bleeding time was observed. A single intravenous dose of DS-1040b after 6 days of clopidogrel treatment was safe and well-tolerated, and no safety concerns were detected.

In an ethnic differences study (DS1040-A-E108) conducted in the United Kingdom, Caucasian, Japanese, Chinese, and Korean subjects (12 subjects each) received a 12-hour intravenous infusion of DS-1040b 20 mg. No ethnic differences in pharmacokinetic parameters were observed. Safety and tolerability were also confirmed in Japanese, Chinese, and Korean subjects.

Currently, Studies DS1040-A-U103 in patients with acute ischemic stroke (ClinicalTrials.gov identifier NCT02586233) and DS1040-B-U107 (NCT02923115) in patients with acute pulmonary embolism are ongoing in the Europe and the United States.

Study DS1040-A-U103, which is ongoing in the United States, the United Kingdom, Germany, and France, is a safety and tolerability study in patients within 4.5 hours to 12 hours after the onset of ischemic stroke. It is an intergroup ascending dose study using a total of 6 cohorts, and DS-1040b is administered intravenously over 6 hours at 6 doses: 0.6, 1.2, 2.4, 4.8, 7.2, and 9.6 mg. Sixteen subjects are enrolled in each cohort (8 or 16 subjects for Cohorts 1 and 2), and are randomized to a DS-1040b or placebo group in a 3:1 ratio. As of Feb 2017, 9 subjects (7 subjects in the United States and 2 subjects in

Germany) have been enrolled in Cohort 1 (0.6 mg), and there have been no safety concerns of DS-1040b, including symptomatic intracranial hemorrhage or treatment-related serious adverse events (SAEs), in these subjects with acute ischemic stroke.

Study DS1040-A-U107, which is ongoing in the United States and EU, is a safety and tolerability study in acute pulmonary embolism patients at moderate risk. There are 6 cohorts in total: 18 subjects are enrolled in each of Cohorts 1 and 2, and are randomized to a DS-1040b or placebo group in a 2:1 ratio, and 20 subjects are enrolled in each of Cohorts 3 to 6, and are randomized to a DS-1040b or placebo group in a 3:1 ratio. There have been no safety concerns of DS-1040b, including SAEs, in these subjects with acute pulmonary embolism.

In the previous clinical studies, no deaths, treatment-related SAEs, or AEs leading to discontinuation have been reported. AEs reported in 2 or more subjects include contact dermatitis (eczema caused by electrocardiogram [ECG]), dyspepsia, ecchymosis (purpura caused by bleeding at the infusion site), and pain in the hands or feet. AEs considered related to the study drug include feeling cold, chilliness, dizziness, and headache, all of which are mild in severity.

1.2.2 Rationale for the Conduct of the Study

In rat models of tail bleeding and cerebral ischemia/reperfusion, no bleeding was observed at higher doses of DS-1040b than those associated with improvement in cerebral blood flow noted in the rat thromboembolic stroke model (3.0 mg/kg). In drug-drug interaction studies with aspirin (DS1040-A-E102) and clopidogrel (DS1040-A-E106) in healthy subjects, DS-1040b was shown not to increase the prolongation of bleeding associated with antiplatelet drugs. These study results suggest that DS-1040b has a low risk of bleeding, indicating that the drug may be used in patients at 4.5 hours or longer after the onset of ischemic stroke who are considered at risk of increased bleeding associated with existing thrombolytic drugs.

Thrombectomy device treatment is approved for patients within 8 hours after the onset of ischemic stroke in principle, with a broader range of patients indicated compared with existing thrombolytic drugs. Furthermore, as methods have been developed to appropriately select the patients with ischemic stroke who are most likely to improve, the number of patients receiving thrombectomy device treatment continues to increase. However, there is a divergence between the rates of recanalization and prognostic improvement, leaving room for improvement, including an increase in the number of patients achieving complete reperfusion. Due to a lower bleeding risk than rt-PAs as suggested by the non-clinical pharmacology study results, DS-1040b can be infused over a longer duration of time than rt-PAs. In combination with a thrombectomy device, DS-

1040b is expected to maintain fibrinolytic activity during treatment, which may result in an increase in the number of patients achieving complete reperfusion and improvement in prognosis after treatment. Therefore, it is important to confirm the safety and tolerability of DS-1040b in combination with a thrombectomy device. In this study, the primary objectives are to confirm the safety and tolerability of DS-1040b in patients with acute ischemic stroke for which thrombectomy device treatment is indicated.

It is also expected that the recurrence of acute ischemic stroke immediately after treatment of the disease may be prevented if the study confirms a persistent effect of continuous treatment with DS-1040b on fibrinolytic biomarkers (sustained inhibition of TAFIa activity and increase in the blood D-dimer level). Therefore, fibrinolytic biomarkers will be assessed as a secondary endpoint in this study.

The results of the recently reported HERMES study show that the incidence of symptomatic intracranial hemorrhage in patients receiving standard drug treatment and patients also receiving thrombectomy device treatment was 4.3% and 4.4%, respectively, indicating a similar rate of bleeding between these two groups of patients.[9] The results of the Rescue-Japan registry show that the incidence of symptomatic intracranial hemorrhage in patients receiving rt-PA therapy combined with endovascular treatment was 7.0% and 3.1% in patients with ICA occlusion and patients with MCA M1 region occlusion, respectively, compared with 4.9% and 3.1%, respectively, among those receiving endovascular treatment alone.[10] These study results suggest that the incidence of symptomatic intracranial hemorrhage is similar between patients receiving standard drug treatment, standard drug treatment in combination with a thrombectomy device, and thrombectomy device treatment alone. It is unlikely that DS-1040b, which is expected to have a lower bleeding risk than existing fibrinolysis activators, will increase the incidence of symptomatic intracranial hemorrhage when used in combination with a thrombectomy device.

Study DS1040-A-U103, which is ongoing in Europe and the United States, is a study intended to confirm the safety and tolerability of DS-1040b in patients within 4.5 hours to 12 hours after the onset of ischemic stroke. Patients in whom standard treatment (rt-PA therapy and thrombectomy device treatment) is indicated, are excluded. There are 6 cohorts in total, and 16 subjects (8 or 16 subjects in Cohorts 1 and 2) are enrolled in each cohort. The sample size was selected based on the results of clinical studies of the standard drug treatment of rt-PA therapy.[11,12] Based on the 16% incidence of symptomatic intracranial hemorrhage in these clinical studies of rt-PA therapy, a sample size that allows the assessment of an incidence of symptomatic intracranial hemorrhage of <= 16% (8 or 16 subjects per cohort, a total of 80 to 96 subjects in all 6 cohorts combined) and the criterion for proceeding to the next cohort (occurrence of two events

of symptomatic intracranial hemorrhage in the DS-1040b group in one cohort) were selected in Study DS1040-A-U103. Since the incidence of symptomatic intracranial hemorrhage in the present study enrolling patients undergoing thrombectomy device treatment alone is expected to be similar to that observed in patients included in Study DS1040-A-U103, it was considered appropriate to use the same sample size for each cohort in the present study as in Study DS1040-A-U103.

The results of the DAWN[13] (2017) and DEFUSE3[14] (2018) studies confirmed that thrombectomy device treatment can be safely achieved up to 24 hours after the onset of ischemic stroke by selecting appropriate patients based on the imaging findings. With the aim of confirming the safety in patients treated with thrombectomy device treatment, which is expected to show a rapid increase in the number of target patients in the future, this study involves patients in principle within 8 hours after the onset of ischemic stroke, the range indicated in the package insert of the thrombectomy device in Japan.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1 Study Objectives

2.1.1 Primary Objectives

This study is a single-blind, intergroup ascending dose study using placebo as a comparator to confirm the safety and tolerability of DS-1040b (0.6, 1.2, 2.4, and 4.8 mg) in patients with acute ischemic stroke in whom thrombectomy device treatment is indicated. The primary endpoints are the incidences of symptomatic intracranial hemorrhage (sICH), asymptomatic intracranial hemorrhage (ICH), and non-intracranial (TIMI) major bleeding.

2.1.2 Secondary Objectives

The secondary endpoints include blood and urine DS-1040a concentrations, change in fibrinolytic biomarkers (TAFIa activity and D-dimer and TAFI antigen levels), change in the NIHSS score at 24 ± 4 hours after the start of study drug administration relative to baseline, and the proportion of subjects with good prognosis (mRS score of 0 to 2) on Days 30 and 90.

2.1.3 Exploratory Objectives

Exploratory endpoints include the proportion of subjects achieving complete reperfusion (TICI grade 3) after thrombectomy device treatment, the effect of DS-1040b on the proportion of subjects with TICI 3, and the effect of DS-1040b on coagulation and fibrinolytic parameters in the fibrin clot structure.

2.2 Study Hypotheses

Not applicable.

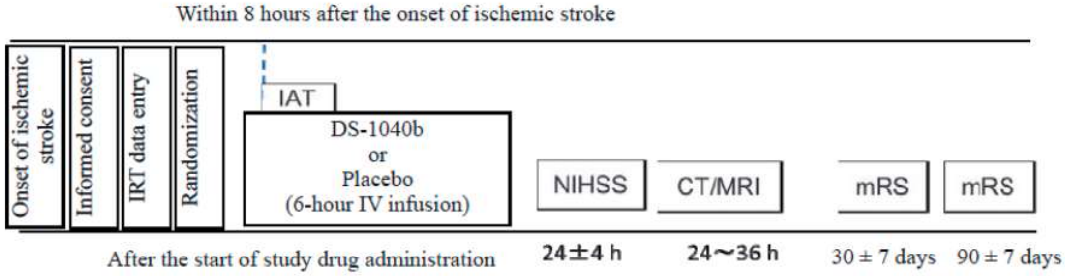
3. STUDY DESIGN

3.1 Overall Design

This study is a multicenter, single-blind, placebo-controlled, randomized, intergroup ascending dose study to confirm the safety and tolerability of DS-1040b in patients with acute ischemic stroke in whom a thrombectomy device is indicated. There will be a total of 4 cohorts, with a planned sample size of 54 or 60 subjects (6 or 12 subjects in the 0.6 mg cohort and 16 subjects per cohort in the other cohorts). The 0.6 mg cohort will only consist of a DS-1040b group. In the other cohorts, subjects will be randomized to the DS-1040b or placebo group in a 3:1 ratio. If any one of the first 6 subjects in the 0.6 mg cohort experiences one event defined as one requiring, "necessary actions to be taken, including discontinuation of the study" as specified in Section 12.4.2, an additional 6 subjects will be enrolled to confirm the safety in a total of 12 subjects. In each cohort, subjects will be evaluated one by one to confirm the absence of symptomatic intracranial hemorrhage through Visit 2 (36 hours after study drug administration) before enrolling the next subject, until 3 subjects aged ≥81 years are enrolled in the DS-1040b group. In each cohort, safety evaluation will be performed when all data collected through Visit 4 (96 hours after study drug administration) are available to determine whether the study should proceed to the next cohort. Subjects will be required to receive inpatient treatment until Visit 4 at the earliest.

The study population consists of patients with acute ischemic stroke in principle within 8 hours after the onset who are not receiving rt-PA therapy, and in whom a thrombectomy device is indicated. Administration of the study drug (the investigational drug or placebo) will in principle be started before recanalization of the occluded vessel after thrombectomy device placement is confirmed (study drug administration will be started immediately if recanalization is achieved before the start of study drug administration). The study drug will be administered as a 6-hour intravenous infusion (25% of the entire amount will be administered intravenously over 30 minutes, followed by 5.5-hour continuous intravenous infusion of the remaining 75% of the injection). Head imaging for assessment of the primary endpoint of intracranial hemorrhage will be performed within 24 hours to 36 hours after the start of study drug administration. As a secondary efficacy endpoint, the change in the NIHSS score at 24 ± 4 hours after the start of study drug administration relative to baseline and the proportion of subjects with good prognosis (mRS score of 0 to 2) on Days 30 and 90 will be assessed (Refer to Figure 3.1-1).

Figure 3.1-1 Flow of Study Procedures Prior to Study Drug Administration and Major Endpoints



3.2 Discussion of Study Design

Randomization will be performed to avoid an imbalance between the placebo and DS-1040b groups. The study will be conducted as a single-blind, intergroup ascending dose study using 4 doses. Assessment bias potentially caused by single-blindness will be avoided by the involvement of a central adjudication committee member who will assess the primary endpoints of symptomatic and asymptomatic intracranial hemorrhage and (TIMI) major bleeding in a blinded fashion. With regard to proceeding to the next cohort, it is considered that the safety of subjects can be ensured by escalating the dose according to the criteria specified in Section 12.4 "Proceeding to the Next Cohort."

4. STUDY POPULATION

The study population will consist of patients with acute ischemic stroke who are not receiving thrombolytic drug therapy and in whom a stent-type thrombectomy device is indicated. Subjects must meet all of the inclusion criteria and not violate any of the exclusion criteria listed below. Subjects must voluntarily provide written informed consent to participate in the study (or the subject's legally acceptable representative must voluntarily provide written informed consent for the subject's participation in the study).

4.1 Inclusion Criteria

Subjects must satisfy all of the following criteria at the time of informed consent to be included in the study:

1) Male or female aged 20 to < 90 years
2) Having acute ischemic stroke with intracranial artery (internal carotid artery [ICA] or middle cerebral artery [MCA] M1 region) occlusion confirmed by computed tomography angiography or magnetic resonance angiography
3) Thrombectomy can be performed in principle within 8 hours after the onset of ischemic stroke.
4) Receiving treatment with a stent-type thrombectomy device as the initial treatment
5) Having an NIHSS score of >= 6 and ASPECTS of >= 6

<Rationale>

1) The legal adult age in Japan is used as the lowest age, and <90 years as the highest age based on the use experience in Study U103, which is ongoing overseas.
2) This criterion will be used to select patients recommended for thrombectomy device treatment by the 2015 ASA/AHA Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment (American Stroke Association [ASA] and American Heart Association [AHA], hereinafter referred to as the "2015 ASA/AHA Guideline").
3) This criterion will be used to select patients in whom a thrombectomy device is indicated.
4) This criterion will be used to achieve the study objectives, that is, the confirmation of the safety and tolerability of DS-1040b in combination with a thrombectomy device as standard treatment
5) This criterion will be used to select patients in whom thrombectomy device treatment is recommended by the 2015 ASA/AHA Guideline.

4.2 Exclusion Criteria

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

study:

1) Having received or planned to receive treatment with a thrombolytic drug (ie, urokinase or rt-PAs)
2) Having Intracranial or subarachnoid hemorrhage confirmed by head imaging (computed tomography [CT] or magnetic resonance imaging [MRI])
3) Having experienced a suspected bleeding event, such as gastrointestinal hemorrhage
4) Having a history of intracranial hemorrhage or a cerebral hemorrhage risk such as intracranial tumor, cerebral aneurysm, and cerebral arteriovenous malformation
5) Having a complication of aortic dissection
6) Having a history of serious head/spinal cord injury or surgery within 3 months
7) Having a history of gastrointestinal or urinary tract hemorrhage within 21 days
8) Having undergone a major surgery or experienced serious non-head injury within 14 days
9) Having activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) of > 2 times the normal value
10) Having an international normalized ratio (INR) of > 1.7
11) Having a platelet count of < 100,000/mm^3
12) Having uncontrolled hypertension despite drug therapy (systolic > 185 mmHg and diastolic > 110 mmHg)
13) Having a baseline blood glucose level of > 400 mg/dL
14) Having occlusion of at least two major arteries
15) Treatment with a stent-type thrombectomy device is not indicated due to the presence of carotid artery dissection, occlusion/vasculitis of the entire carotid artery/neck, contrast media allergy, etc.
16) Having a severe hepatic disorder (fulminant hepatitis, hepatic cirrhosis, hepatic tumor, or other hepatic disorders meeting any of the following criteria)

Parameter	Criterion
Total bilirubin	>= 3.0 mg/dL
AST (GOT)	>= 2.5 × the upper limit of reference range or >= 100 U/L
ALT (GPT)	>= 2.5 × the upper limit of reference range or >= 100 U/L
ALP	>= 2.5 × the upper limit of reference range

17) Being on chronic dialysis or having a severe renal disorder (eg, nephrotic syndrome, acute/chronic renal failure, uremia, and hydronephrosis) or a serum creatinine level of >= 2 mg/dL
18) Having a history of ischemic stroke within 30 days prior to the study drug

administration

19) Having received another study drug in another clinical study within 30 days prior to the study drug administration in this study
20) Being pregnant, having the potential of being pregnant, being breastfeeding, or planning to become pregnant (or having a partner who is planning to become pregnant) while participating in the study
21) Otherwise considered inappropriate for the study by the investigator or subinvestigator

<Rationale>

1) This criterion will be used because the safety of subjects cannot be ensured with absolute certainty due to insufficient data on the assessment of the bleeding risk associated with the combined use of DS-1040b and rt-PA therapy.
2) to 3) These criteria will be used because a potential worsening of existing bleeding events associated with the use of DS-1040b cannot be ruled out.
4) to 13) These criteria will be used to exclude patients at a high bleeding risk.
14) This criterion will be used in consideration of the potential effect of DS-1040b on the TICI grade as a reperfusion marker index.
15) This criterion will be used to appropriately enroll patients in whom stent placement is indicated.
16) to 18) These criteria will be used in consideration of the safety of subjects.
19) This criterion will be used in consideration of ethics and the safety of subjects.
20) This criterion will be used in consideration of ethics and the safety of subjects. Contraception with the use of the barrier method (spermicide condoms, intrauterine device, etc., approved or certified in Japan) will be required for at least 90 days after study drug administration.
21) This criterion will be used to allow the investigator or subinvestigator to determine the eligibility of subjects by taking other general factors into account.

5. STUDY TREATMENT(S)

5.1 Assigning Subjects to Treatments and Blinding

5.1.1 Treatment Groups

Four doses of DS-1040b on a free-form (DS-1040a) equivalent basis will be studied: 0.6, 1.2, 2.4, and 4.8 mg. Each dose will be administered intravenously over 6 hours. Subjects randomized to the placebo group will receive 6-hour intravenous infusion of saline not containing DS-1040b Injection 10 mg/10 mL. Details of the dosing regimen are provided below.

The required amount of DS-1040b Injection 10 mg/10 mL will be removed from the vial and added to 100 mL of saline. One-fourth (25%) of the entire amount will be administered intravenously over 30 minutes as a loading dose, followed by a 5.5-hour continuous intravenous infusion of the remaining three-fourths of the injection (75%) as a maintenance dose. Administration of the loading dose will in principle be started before recanalization of the occluded vessel is achieved with a thrombectomy device; however, it may be started immediately after recanalization if it is likely to be achieved prior to study drug administration.

Table 5.1-1 Dose Level and Predicted Blood Concentrations for Each Cohort

Cohort	Dose (mg)	Preparation		Infusion Rate for the Loading Dose (30-minute Intravenous Infusion of 25% of the Entire Amount)	Infusion Rate for the Maintenance Dose (5.5-hour Intravenous Infusion of 75% of the Entire Amount)	CLcr (mL/min)	Predictive Value Obtained Using Data from the Single-dose Study in Healthy Subjects			
		Drug Solution Volume (mL)	0.9% Saline (mL)				$C_{0.5h}$ (ng/nL)	Cmax (ng/mL)	Tmax (h)	AUC (ng·h/mL)
1	0.6	0.6	100	0.84 mL/min	0 23 mL/min	60	14.3	15.8	6	144
						90	13.9	13.9	0.5	118
						120	13.6	13.6	0.5	100
2	1.2	1.2	100	0.84 mL/min	0 23 mL/min	60	28.6	31.7	6	288
						90	27.9	27.9	0.5	236
						120	27.2	27.2	0.5	200
3	2.4	2.4	100	0.85 mL/min	0 23 mL/min	60	57.2	63.4	6	576
						90	55.8	55.8	0.5	472
						120	54.5	54.5	0.5	400
4	4.8	4.8	100	0.87 mL/min	0 24 mL/min	60	114	127	6	1151
						90	112	112	0.5	944
						120	109	109	0.5	800

<Rationale>

In Study DS1040-A-U101 in healthy subjects, the IC_{90} value in clot lysis assay was reported to be 38.2 ng/mL. Based on the results of modeling and simulation (M&S) constructed using data from the single-dose study in healthy subjects (DS1040-A-U101), the Cmax value in subjects with body weight of 60 kg was predicted to be 23.8 ng/mL to 31.7 ng/mL for Cohort 2 (DS-1040b 1.2 mg), indicating that the dose level in Cohort 2 is

expected to provide increased endogenous fibrinolytic activity. Due to the lack of clinical experience with DS-1040b in Japanese patients with acute ischemic stroke in whom a thrombectomy device is indicated, the dose level in Cohort 1 (DS-1040b 0.6 mg) will be used as a starting dose to confirm the safety of DS-1040b in this study.

In the drug-drug interaction study with aspirin (DS1040-A-E102), Cmax and AUC of DS-1040a following 6-hour intravenous infusion of DS-1040b 6 mg were 582 ng/mL and 1118 h·ng/mL, respectively, indicating that DS-1040b does not increase the prolongation of bleeding associated with aspirin under these conditions. In the drug-drug interaction study with clopidogrel (DS1040-A-E106), Cmax and AUC of DS-1040a following 12-hour intravenous infusion of DS-1040b 20 mg were 290 ng/mL and 3670 h·ng/mL, respectively, indicating that DS-1040b does not increase the prolongation of bleeding associated with clopidogrel under these conditions. In the drug-drug interaction study with enoxaparin (DS1040-A-U104), Cmax and AUC of DS-1040a following 12-hour intravenous infusion of DS-1040b 20 mg were 304 ng/mL and 4079 h·ng/mL, respectively, confirming the safety and tolerability of DS-1040b.

Cmax and AUC in Cohort 4 (DS-1040b 4.8 mg) were predicted to be 95.3 ng/mL to 127 ng/mL and 800 h·ng/mL to 1151 h·ng/mL, respectively, suggesting that the dose level in Cohort 4 may also be associated with a low bleeding risk. Thus, doses ranging from 0.6 mg to 4.8 mg will be used in this study.

5.1.2 Method of Randomization

The independent biostatistician will prepare a randomization schedule as instructed by the sponsor. In Cohorts 2 to 4, subjects will be randomized to the DS-1040b or placebo group in a 3:1 ratio using block randomization. The study drug with the same drug number will be used exclusively for one subject and will not be used for any other subjects.

Subjects will be enrolled in the study via the web-based interactive response technology (IRT) system. The procedures for subject enrollment are shown in Figure 5.1-1.

After obtaining written informed consent from each subject (or his/her legally acceptable representative), the investigator or subinvestigator will prepare the subject screening list and assess the subject's eligibility.

The investigator, subinvestigator, or study staff will enter the required information of subjects from whom informed consent has been obtained into the IRT system. A study-specific subject number will be assigned by the IRT system. The investigator, subinvestigator, or study staff will then enter the subject's eligibility assessment result into the IRT system. Via the IRT system, randomization of subjects assessed as eligible

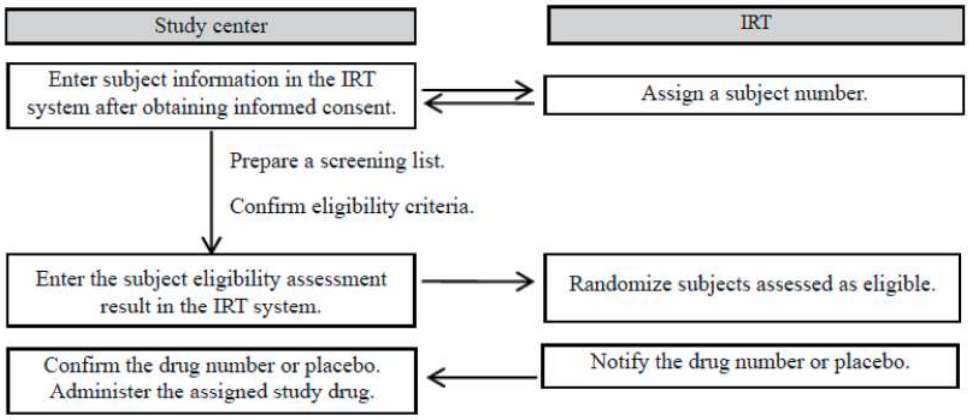
will be performed. If the subject is randomized to the DS-1040b group, a drug number will be notified by the IRT system. If the subject is randomized to the placebo group, the term "placebo" will be displayed.

Based on the results of randomization on the IRT system, DS-1040b or placebo with a drug number displayed on the system should be prepared at the required dose to start study drug administration. The date of randomization will be defined as the date of enrollment.

The investigator or subinvestigator will explain the reason for ineligibility to each subject assessed as ineligible by the investigator or subinvestigator, and initiate alternative treatment. The investigator or subinvestigator will also record the reason for not enrolling the subject in the subject screening list.

If study drug administration cannot be started after randomization due to, for example, a sudden change in the health condition of the subject, the date of and reason for dropout will be recorded in the case report form (CRF).

Figure 5.1-1 Procedures for Subject Enrollment in Each Cohort



5.1.3 Blinding

This study will be conducted as a single-blind study, in which subjects will be blinded.

5.1.4 Emergency Unblinding Procedure

Not applicable because this is a single-blind study.

5.2 Study Drug

5.2.1 Description

The study drug is an injectable solution filled in a glass vial. Each vial containing DS-1040b 10 mg (DS-1040b Injection 10 mg/10 mL) is packaged in a box and will be supplied by the sponsor. For the details and handling of the study drug, refer to the Investigator's Brochure and the Procedures for Study Drug Management.

1) Active ingredient code: DS-1040b
2) Nonproprietary name: To be determined.
3) Content and dosage form: A colorless clear aqueous injectable solution containing 10 mg of the active ingredient (DS-1040a) filled in each 10 mL container
4) Lot number: Provided in the Procedures for Study Drug Management.

5.2.2 Labeling and Packaging

Each vial containing the study drug (DS-1040b Injection 10 mg/10 mL) is packaged in a box. A study drug label is attached to each vial and box. Detailed information to be contained on the label is provided in Table 5.2-1.

Table 5.2-1 Information on the Study Drug Label

Labeled as "For Clinical Study Use"

Protocol number
Drug number
Study drug lot number
Storage conditions
Name of the sponsor
Address of the sponsor

5.2.3 Preparation

The instructions for study drug preparation are outlined below. For details, refer to the Procedures for Study Drug Management.

The amount of DS-1040b Injection 10 mg/10 mL specified in Table 5.2-2 should be added in a 100 mL saline bag and be mixed well.

Table 5.2-2 Preparation of Drug Solution

Cohort	Dose	Preparation		Total
		DS-1040b Injection 10 mg/10 mL	Saline	
1	0.6 mg	0.6 mL	100 mL	100.6 mL
2	1.2 mg	1.2 mL	100 mL	101.2 mL
3	2.4 mg	2.4 mL	100 mL	102.4 mL
4	4.8 mg	4.8 mL	100 mL	104.8 mL

In-use stability (storage of the prepared study drug)

1) Stored at room temperature (1°C to 30°C).
   Administration of the prepared study drug should be completed within 12 hours after the start of preparation.
2) Refrigerated (2°C to 8°C).
   The study drug should be refrigerated (2°C to 8°C) immediately after preparation. The study drug is usable for 24 hours if it is administered immediately after removing it from the refrigerator (administration of the study drug should be completed within 12 hours after the start of preparation).

5.2.4 Administration

Using an infusion pump, one-fourth (25%) of the entire amount will be administered intravenously over 30 minutes, followed by a 5.5-hour continuous intravenous infusion of the remaining injection. The infusion rate in each cohort is shown in Table 5.2-3. Administration of the study drug should in principle be started before recanalization of the occluded vessel is achieved with a stent-type thrombectomy device. However, it may be started immediately after recanalization if recanalization is likely to be achieved prior to study drug administration.

Table 5.2-3 Infusion Rate

Cohort	Dose	Infusion Rate	
		Loading Dose	Maintenance Dose
1	0.6 mg	0.84 mL/min	0.23 mL/min
2	1.2 mg	0.84 mL/min	0.23 mL/min
3	2.4 mg	0.85 mL/min	0.23 mL/min
4	4.8 mg	0.87 mL/min	0.24 mL/min

5.2.5 Storage

Stored at room temperature (1°C to 30°C).

The study drug will be stored at room temperature (1°C to 30°C) in a safe storage area with limited access. In the event of deviation from the specified storage conditions, it should immediately be reported to the sponsor according to the Procedures for Study Drug Management.

5.2.6 Drug Accountability

The instructions for study drug management are outlined below. For details, refer to the Procedures for Study Drug Management.

When a drug shipment is received, the study drug manager or a designee will check the amount and condition of the drug, check the appropriateness of the label, drug expiration date, and sign the Receipt of Shipment Form provided.

The signed "Receipt of Shipment Form" will be returned to the sponsor, and a photo copy will be kept at the study center.

In addition, the study drug manager or a designee will contact the sponsor as soon as possible if there are any problems with the study drug.

The Drug Accountability Record must be kept current and should contain the dates and quantities of the study drug received, the subject (identification number) for whom the study drug was dispensed, the date and quantity of the study drug dispensed and remaining, as well as the signature, initials, or seal of the dispenser.

At the end of the study, or as directed, all DS-1040b Injection 10 mg/10 mL after resolving any discrepancies, including unused drug, will be returned to the designee as instructed by the sponsor. Study drug will be returned only after the clinical research associate has completed the final inventory to verify the quantity to be returned. The return of study drug must be documented and the documentation must be included in the shipment. At the end of the study, a final study drug reconciliation statement (Study Drug Return Form and Study Drug Accountability Log [copies]) must be completed by the study drug manager or a designee and provided to the sponsor.

5.3 Control Treatment

In this study, only the investigational drug (DS-1040b Injection 10 mg/10 mL) will be supplied by the sponsor.

For details, including the handling of the investigational drug, refer to the Procedures for Study Drug Management.

5.4 Dose Interruptions and Reductions

Not applicable.

5.5 Method of Assessing Treatment Compliance

Information on study drug administration, including the date and the start and end times of study drug administration, will be recorded in the CRF.

5.6 Prior and Concomitant Medications

5.6.1 Prior Treatment

For any antiplatelet or anticoagulant drug used within 2 weeks before the day of informed consent, the drug name, dosage regimen, the start and end dates of treatment, and the reason for use will be recorded in the CRF.

5.6.2 Concomitant Drugs

A concomitant drug is defined as any non-study drug used at any time between the day of informed consent and Visit 4 (96 hours after study drug administration). Concerning any concomitant drugs used, the drug name, dosage regimen, start and end dates of treatment, and the reason for use will be recorded in the CRF. Diagnostic agents, nutrition formulations, intravenous fluids (for rehydration), and antiseptics used for any other purposes than the treatment of AEs will not be recorded in the CRF. However, these drugs will be recorded in the CRF if they are used at Visit 1 or are considered responsible for the occurrence of AEs (eg, contrast media allergy).

5.6.3 Prohibited Concomitant Drugs

The following treatments will be prohibited for 24 hours after the start of study drug administration:

1) Thrombolytic drugs (urokinase, rt-PAs)
2) Dual antiplatelet therapy (DAPT)
3) Antiplatelet drugs (excluding aspirin and clopidogrel)
4) Drugs that inhibit platelet aggregation
5) Anticoagulant drugs (excluding enoxaparin and heparin used during

thrombectomy device treatment)

Table 5.6-1 Prohibited Concomitant Drugs

Drug Type	Drug Name (Examples)
1) Thrombolytic drugs	Urokinase, t-PAs, etc.
2) Dual antiplatelet therapy	-
3) Antiplatelet drugs	Prasugrel hydrochloride, ticlopidine hydrochloride, ozagrel sodium, ozagrel hydrochloride, cilostazol
4) Drugs that inhibit platelet aggregation (including acidic nonsteroidal anti-inflammatory drugs)	PGE_1 preparations, PGI_2 preparations, ethyl icosapentate, sarpogrelate hydrochloride, dipyridamole, trapidil, dilazep hydrochloride, trimetazidine hydrochloride, etc. Loxoprofen sodium hydrate, indometacin, diclofenac sodium, mefenamic acid, ibuprofen, etc.
5) Anticoagulant drugs	Warfarin, dabigatran, rivaroxaban, apixaban, batroxobin, fondaparinux, argatroban, gabexate mesilate, nafamostat mesilate, freeze-dried concentrated human antithrombin III, freeze-dried concentrated human activated protein C, etc.

<Rationale>

1) A bleeding risk associated with the combined use of a thrombolytic drug and DS-1040b cannot be ruled out.
2) The bleeding risk during DAPT is unknown, although the combined use of an antiplatelet drug (aspirin or clopidogrel) and DS-1040b is likely to be highly safe based on the following study results:

✓ No prolongation of bleeding time was observed, as shown by bleeding time measurement using the Surgicutt method, in Study DS1040-A-E102, in which healthy adults received aspirin 300 mg for 4 days, followed by coadministration of aspirin 300 mg and DS-1040b 6 mg (30-minute intravenous infusion) on Day 5.

✓ No prolongation of bleeding time was observed, as shown by bleeding time measurement using the Surgicutt method, in Study DS1040-A-E106, in which healthy adults received clopidogrel (at loading and maintenance doses of 300 mg and 75 mg, respectively) for 5 days, followed by coadministration of clopidogrel 75 mg and DS-1040b 20 mg (12-hour intravenous infusion) on Day 6.

3) 4) 5) A bleeding risk associated with the combined use with DS-1040b cannot be ruled out.

5.6.4 Other Restrictions

Elective surgery should not be performed within 5 days after study drug administration (day of study drug administration plus 5 days). However, this does not prevent emergency surgery indicated to treat the subject. The appropriateness of surgery should be determined based on careful assessment of the risks and benefits.

<Rationale>

While non-clinical studies as well as clinical studies in healthy adults have shown that DS-1040b does not prolong bleeding time, a possible effect on bleeding has not been ruled out completely. To avoid an unnecessary bleeding risk, non-urgent elective surgery is contraindicated within 5 days after study drug administration. The reason for setting the period of 5 days is that the plasma DS-1040a concentration decreased to less than 10% within 12 hours after the end of the infusion(*), suggesting that it would have disappeared from the plasma in 5 days.

(*) Data from Study DS1040-A-U101

5.7 Subject Withdrawal/Discontinuation

5.7.1 Reasons for Withdrawal

If a subject meets any of the following items, the investigator or subinvestigator will immediately withdraw the subject from the study and record the reason for withdrawal in the CRF, and will take appropriate actions for the subject. If abnormalities in test values, etc. are observed at the time of withdrawal, the investigator or subinvestigator will follow the subject's course until such abnormalities have normalized or returned to the baseline level and to an extent that the subject's cooperation can be obtained, perform the medical examinations and tests specified in the protocol, and make all efforts to ensure the subject's safety.

Information of each subject including study completion or withdrawal, date of study completion or withdrawal, and the reason for withdrawal will be recorded in the CRF.

- The subject or his/her legally acceptable representative requests to be withdrawn from treatment.
- The subject receives treatment with any existing thrombolytic drugs (urokinase or rt-PAs) or the need for such treatment arises before or during study drug administration.
- Treatment with a stent-type thrombectomy device is no longer required.
- The need for DAPT arises before or during study drug administration.
- Continuation of the study is not judged to be preferable because of an AE.
- The subject misses a hospital visit.
- The subject is found not to meet all of the inclusion criteria or is found to violate any of the exclusion criteria.
- The investigator or subinvestigator deems that continuation of treatment is inappropriate for another reason.

- The sponsor decides to discontinue the study.

5.7.2 Withdrawal Procedures

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

- If the decision on study discontinuation is made before Visit 2 assessment
  As the assessment at discontinuation, the Visit 2 assessment should be performed within 24 hours to 36 hours after the start of study drug administration.
- If the decision on study discontinuation is made after the completion of Visit 2 assessment but before Visit 4 assessment
  As the assessment at discontinuation, the Visit 4 assessment should be performed within 96 ± 12 hours after the start of study drug administration.

If the study is discontinued after Visit 4, the assessment at discontinuation will not be required.

Follow-up on Visits 5 and 6 will in principle be performed for all subjects, including those withdrawn from the study.

If the subject is withdrawn due to an AE, the investigator or subinvestigator will follow the subject until the AE has resolved or stabilized.

6. STUDY PROCEDURES

6.1 Screening and Randomization (Prior to the Start of Study Drug Administration)

- Obtain the subject's signature on the informed consent form (ICF).
- At the study center(s) participating in the gene banking research, obtain the subject's signature on the ICF for the gene banking research (which is optional and will be performed by Visit 4).
- Review inclusion/exclusion criteria.
- Perform head imaging (CT or MRI).
- Record baseline subject characteristics.
- Collect information on complications, concomitant drugs, smoking habit, height, and body weight as far as possible. Any uncollected information should be collected and recorded in the CRF as soon as possible after acute-phase treatment.
- Record the pregnancy test result, as appropriate (the test date and results).
- Record vital signs (blood pressure, pulse rate).
- Perform 12-lead ECG.
- Perform hematology, blood chemistry, and blood coagulation (local) tests.
- Record the baseline NIHSS score.
- Collect blood for the blood coagulation test, and pharmacodynamic and pharmacokinetic assays performed at the central laboratory.

6.2 Visit 1 (Day of Study Drug Administration)

- Administer the study drug, and record the start and end times of study drug administration
- Perform thrombectomy device treatment, and record the details (refer to Section 6.19 "Cerebral Artery Revascularization").
- After the completion of thrombectomy device treatment, record the TICI grade and the NIHSS score obtained immediately after the treatment.
- Collect and record information on AEs and any intervention for the AEs (drug and non-drug therapy).
- Record concomitant drugs.
- Perform hematology, blood chemistry, and blood coagulation (local) tests at 6 hours (-5 minutes) after the start of study drug administration, and record the test results.
- Collect blood for a blood coagulation test performed at the central laboratory at 6 hours (-5 minutes) after the start of study drug administration.
- Collect blood for pharmacodynamic assay at 6 hours (-5 minutes) after the start of

study drug administration.

- Collect blood for pharmacokinetic assay at 0.5 hours (-5 minutes), 3 hours (±10 minutes), and 6 hours (-5 minutes) after the start of study drug administration. Collect blood at 18 hours (±10 minutes) after the start of study drug administration as far as possible.
- Collect urine for 24 hours after the start of study drug administration for pharmacokinetic assay.

6.3 Visit 2

- Record concomitant drugs.
- Collect and record information on AEs and any intervention for the AEs (drug and non-drug therapy).
- Perform head imaging (CT or MRI) within 24 hours to 36 hours after the start of study drug administration.
- Perform the NIHSS assessment and record the results at 24 ± 4 hours after the start of study drug administration.
  Perform vital sign measurement (blood pressure and pulse rate), 12-lead ECG, and hematology, blood chemistry, and blood coagulation (local) tests at 24 ± 12 hours after the start of study drug administration, and record the results.
- Collect blood for a blood coagulation test performed at the central laboratory at 24 hours (±10 minutes) after the start of study drug administration.
- Collect blood for pharmacodynamic assay at 24 hours (±10 minutes) after the start of study drug administration.
- Collect blood for pharmacokinetic assay at 24 hours (±10 minutes) after the start of study drug administration.

6.4 Visit 3

- Record concomitant drugs.
- Collect and record information on AEs and any intervention for the AEs (drug and non-drug therapy).
- Measure vital signs (blood pressure and pulse rate) at 48 ± 12 hours after the start of study drug administration, and record the results.
- Collect blood for pharmacodynamic assay at 48 hours (±15 minutes) after the start of study drug administration.
- Collect blood for pharmacokinetic assay at 48 hours (±15 minutes) after the start of study drug administration.

6.5 Visit 4

- Record concomitant drugs.
- Collect and record information on AEs and any intervention for the AEs (drug and non-drug therapy).
- Perform vital sign measurement (blood pressure and pulse rate), and hematology and blood chemistry tests at 96 ± 12 hours after the start of study drug administration, and record the results.
- Collect blood for a blood coagulation test performed at the central laboratory at 96 hours (±15 minutes) after the start of study drug administration.
- Collect blood for pharmacokinetic assay at 96 hours (±15 minutes) after the start of study drug administration.

6.6 At the Onset of Intracranial Hemorrhage (If Observed Within 96 Hours after the Start of Study Drug Administration)

- Perform head imaging (CT or MRI).
- Record the NIHSS score.

6.7 Visit 5 to Visit 6 (Follow-up)

- Perform follow-up twice, namely, on Days 30 ± 7 and 90 ± 7.
- Collect and record information on AEs and any intervention for the AEs (drug and non-drug therapy).
- Follow-up via telephone, etc., will also be acceptable.
- Record the mRS score.
- Determine the presence or absence of any new cerebrovascular accidents that occur after Visit 4. Record information on the event, if any, including the date of onset and the event term (ischemic stroke, intracranial hemorrhage, and others).

6.8 List of Study Procedures

Study procedures and the schedule of each study procedure are shown in Table 6.8-1 and Appendix 1, respectively.

The investigator, subinvestigator, or study staff will determine whether the subject is receiving treatment at another department of the study center or another hospital.

Table 6.8-1 List of Study Procedures

Study Procedure	
Informed consent	Date of informed consent
Baseline subject characteristics	Date of birth, sex, the site of occlusion, ASPECTS (score, equipment used [CT or MRI]), complications, medical history of ischemic stroke/TIA and intracranial hemorrhage, concomitant drugs, smoking habit, pregnancy test result (if applicable), and a change in the therapeutic category
Inclusion/exclusion criteria	Compliance with the inclusion/exclusion criteria (If any inclusion/exclusion criteria are not met, provide each relevant criterion, the criterion number, and the protocol version number.)
Physical examination and medical interview	Date of physical examination, the presence or absence of AEs
Height, body weight, and vital signs	Height, body weight, BMI (calculated from the subject's height and body weight), blood pressure, pulse rate
Head imaging	CT or MRI and angiography of the head
ECG	12-lead ECG
Laboratory tests	
Hematology test	Red blood cell count, hemoglobin, hematocrit, white blood cell count, white blood cell differential (neutrophil, lymphocyte, monocyte, eosinophil, basophil), platelet count
Blood chemistry test	Total protein, albumin, A/G ratio, total bilirubin, direct bilirubin, AST, ALT, ALP, γ-GT, LDH, CK, BUN, creatinine, uric acid, Na, K, Cl, Ca, P, Mg, total cholesterol, triglyceride, glucose, CRP
Blood coagulation test (local)	PT, INR, aPTT
Blood coagulation test (central)	PT, INR, aPTT, fibrinogen
Neurological Symptoms	NIHSS, mRS
Pharmacokinetics	Plasma and urine drug concentrations
Pharmacodynamics (biomarkers)	TAFIa activity, D-dimer level, TAFI antigen level, and a change in coagulation and fibrinolytic parameters in the fibrin clot structure
Pharmacogenomics	Gene banking

6.9 Baseline Subject Characteristics

The investigator or subinvestigator will collect the following information before the start of study drug administration, and record it in the CRF:

- Date of informed consent, date of birth, sex, the site of occlusion, and ASPECTS (score, equipment used [CT or MRI])

After acute-phase treatment, the following information will also be collected and recorded in the CRF as soon as possible:

- Complications (findings/diagnosis and the date of diagnosis), medical history of ischemic stroke/TIA and intracranial hemorrhage, prior treatment/concomitant drugs (the drug name, dosage regimen, start and end dates of treatment, and the reason for use), smoking habit (presence or absence), and a change in the therapeutic category (presence or absence, change, and date of the change)

If there are any changes in the inpatient/outpatient therapeutic category, the following information will be recorded in the CRF:

- Changes in the therapeutic category (change and date of the change)

The investigator, subinvestigator, or study staff will determine whether the subject is receiving treatment at another department of the study center or another hospital.

6.10 Physical Examination and Medical Interview

The presence or absence of AEs before the start of study drug administration and dates of physical examination at Visits 2, 3, 4, 5, and 6 will be recorded in the CRF.

6.11 Height, Body Weight, and Vital Signs

Height and body weight will be measured before Visit 4, and the results and date of measurement will be recorded in the CRF. For blood pressure and pulse rate, the presence or absence of measurements and the results and date/time of measurements will be recorded in the CRF before the start of study drug administration and at Visits 2, 3, and 4.

6.12 Pregnancy Test

A pregnancy test will be performed in premenopausal female subjects before the start of study drug administration. Either a blood test or a urinalysis will be acceptable. The date and result of the test will be recorded in the CRF.

6.13 Head Imaging (CT or MRI)

Diagnostic imaging will be performed before the start of study drug administration, within 24 to 36 hours after the start of study drug administration, and at the onset of intracranial hemorrhage (within 96 hours after the start of study drug administration). The primary objective of this diagnostic imaging is to determine the presence or absence of bleeding. The following information will be recorded in the CRF:

Equipment used (CT or MRI), the date of testing, and the presence or absence of intracranial hemorrhage

The image data need to be submitted to the sponsor for the assessment of intracranial hemorrhage classification by the central adjudication committee member. For subjects transported from another hospital, it is not necessary to obtain new image data if image data for submission are available.

6.14 Electrocardiogram

Findings of 12-lead ECG obtained before the start of study drug administration and at Visit 2 will be assessed as “normal,” “abnormal, not clinically significant,” or “clinically

significant." The assessment and the date/time of measurement will be recorded in the CRF. If assessed as "clinically significant, it should be determined whether the finding is regarded as an AE. Findings that have already been noted prior to study drug administration and have not worsened after study drug administration will not be regarded as AEs. For findings regarded as AEs, the event will be recorded in the CRF.

6.15 Laboratory Tests

The parameters listed below will be measured before and at 6 hours after the start of study drug administration, at Visits 2 and 4, and at the time of discontinuation, and the presence or absence of measurements, the date/time of blood collection, and the measurement results will be recorded in the CRF. Each study center's reference ranges will be used for laboratory data.

- Hematology test: red blood cell count, hemoglobin, hematocrit, white blood cell count, white blood cell differential (neutrophil, lymphocyte, monocyte, eosinophil, basophil), platelet count
- Blood chemistry test: total protein, albumin, A/G ratio, total bilirubin, direct bilirubin, AST, ALT, ALP, γ-GT, LDH, CK, BUN, creatinine, uric acid, Na, K, Cl, Ca, P, Mg, total cholesterol, triglyceride, glucose, CRP

6.16 Blood Coagulation Test

Blood coagulation parameters (PT, INR, aPTT, and fibrinogen) will be measured at the central laboratory before and at 6 hours after the start of study drug administration and at Visits 2 and 4. The date/time of blood collection will be recorded in the CRF. For safety confirmation, blood coagulation parameters (PT, INR, and aPTT) will also be measured at each study center before and at 6 hours after the start of study drug administration and at Visit 2, and the presence or absence of measurements, the date/time of blood collection, and the measurement results will be recorded in the CRF. Each study center's reference ranges will be used for blood coagulation parameters measured at each study center.

6.17 Neurological Symptoms (National Institute of Health Stroke Scale)

The NIHSS assessment will be performed before the start of study drug administration, immediately after thrombectomy device treatment, at 24 ± 4 hours after the start of study drug administration, and at the onset of intracranial hemorrhage, and the NIHSS score and the date/time of assessment will be recorded in the CRF. In the event of intracranial hemorrhage, the NIHSS score and the date/time of assessment should immediately be recorded in the CRF, and it should be confirmed whether the event is a symptomatic intracranial hemorrhage.

6.18 Neurological Symptoms (modified Rankin Scale)

The mRS assessment will be performed at Visit 5 (Day 30 ± 7) and Visit 6 (Day 90 ± 7), and the method, date, and results of assessment will be recorded in the CRF.

Table 6.18-1 Modified Rankin Scale

Grade 0	No symptoms at all
Grade 1	No significant disability despite symptoms; able to carry out all usual duties and activities
Grade 2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
Grade 3	Moderate disability; requiring some help, but able to walk without assistance
Grade 4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
Grade 5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
Grade 6	Dead

6.19 Cerebral Artery Revascularization (Mechanical Thrombectomy or Local Intra-arterial Thrombolysis)

For any mechanical thrombectomy or local intra-arterial thrombolysis performed on cerebral arteries at any time between the day of informed consent and Visit 4 (96 hours after the start of study drug administration), the details listed below will be recorded in the CRF.

The date/time of the onset of ischemic stroke, visit, and puncture, the site of puncture, the size of the guiding catheter, the date/time of the initial device delivery (the start of intra-arterial injection), the date/time of recanalization of the occluded vessel, the site of vascular occlusion, the TICI grade (assessment date/time and results), the type of the device used (thrombolytic drugs), and the presence/absence and the type of an additional device.

If the accurate date/time of the onset of ischemic stroke cannot be identified, the date when the subject was last confirmed to be healthy will be recorded. If thrombectomy is considered feasible based on the imaging findings although it is more than 8 hours after the time when the subject was last confirmed to be healthy, it should be recorded.

The TICI grade will be determined according to Table 6.19-1. The image data used for the final assessment will be submitted to the sponsor.

Table 6.19-1 TICI Grades

0	No perfusion
1	Recanalization achieved but with no or slow peripheral perfusion

2A	Perfusion achieved in half or less of the vascular territory
2B	Perfusion achieved in half or more of the vascular territory
3	Complete perfusion with peripheral perfusion

6.20 Other Surgical Procedures for Cerebrovascular Accidents

For any of the following surgical procedures performed at any time between the day of informed consent and Visit 6 (Day 90), the date/time of the procedure will be recorded in the CRF:

1) Carotid artery stenting
2) Carotid endarterectomy
3) Bypass surgery
4) Surgery for cerebral aneurysm (eg, surgical clipping, coil embolization)
5) Surgery for intracranial hemorrhage (eg, hematoma evacuation, hematoma aspiration)

7. PRIMARY ENDPOINTS

The primary endpoints of this study are the incidences of the following bleeding events, because safety confirmation is the primary objective of this study:

- Symptomatic intracranial hemorrhage confirmed within 36 hours after the start of study drug administration

  Intracranial hemorrhage with clinical deterioration causing an increase in the NIHSS score of >= 4 points (defined by ECASS)

- Asymptomatic intracranial hemorrhage confirmed within 36 hours after the start of study drug administration

  All events of intracranial hemorrhage other than the above-mentioned symptomatic intracranial hemorrhage, and will be classified as follows:

  1) Hemorrhagic infarction type 1 (HI1) Small petechial hemorrhage along the margins of the infarct
  2) Hemorrhagic infarction type 2 (HI2) Confluent petechial hemorrhage within the infarcted area, but without a mass effect
  3) Parenchymal hematoma type 1 (PII1) IIematoma involving <= 30% of the infarcted area with a slight mass effect
  4) Parenchymal hematoma type 2 (PH2) Hematoma involving > 30% of, or outside the infarcted area, with a significant mass effect

- Non-intracranial (TIMI) major bleeding confirmed within 96 hours after the start of study drug administration

  Clinically evident bleeding with a 5 g/dL or greater decrease in hemoglobin
  A 2-unit (1 unit is equivalent to 200 mL) blood transfusion will be converted to a 1 g/dL increase in hemoglobin.

8. EFFICACY ASSESSMENTS

The following efficacy endpoints will be assessed:

1) Change in the NIHSS score at 24 ± 4 hours after the start of study drug administration relative to baseline
2) Proportion of subjects with good prognosis (mRS score of 0 to 2) on Days 30 and 90
3) TICI grade obtained immediately after thrombectomy device treatment

9. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

9.1 Pharmacokinetic Endpoints

The pharmacokinetic parameters listed below will be calculated from plasma and urine concentrations of DS-1040a using a non-compartment method.

[Pharmacokinetic parameters]

Cmax, Tmax, AUClast, $T_{1/2}$, cumulative urinary excretion, cumulative urinary excretion rate (% of dose), and CLr

The procedures for the handling of specimens will be detailed in the separately prepared "Procedures for Handling of Specimens for Drug Concentration Measurement."

9.1.1 Collection of Plasma Specimens

Blood collection time points: Before the start of study drug administration and at 0.5 hours (−5 minutes), 3 hours (±10 minutes), 6 hours (−5 minutes), 18 hours (±10 minutes), 24 hours (±10 minutes), 48 hours (±15 minutes), and 96 hours (±15 minutes) after the start of study drug administration
A total of 8 time points (The time point of 18 hours after the start of study drug administration should in principle not be skipped.)

Blood collection volume: 3 mL/collection

Using a vacuum blood collection tube (with K_2EDTA), venous blood will be collected (arterial blood is also acceptable). Each tube will be mixed by inversion immediately after blood collection. The tube will then be centrifuged at 1500 × g for 15 minutes. The separated plasma will swiftly be aliquoted into two storage vials and stored at −20°C or lower until shipment to the drug concentration measurement laboratory. The process from blood collection to cryopreservation should be performed within 24 hours. The investigator or subinvestigator will record the date/time of blood collection in the CRF.

9.1.2 Collection of Urine Specimens

Urine collection time points: From the start of study drug administration to 24 hours after study drug administration (pooled urine)

During urine collection, the entire urine collected will be transferred to a urine container. The collected urine specimen will swiftly be aliquoted into two storage vials (10 mL each) and stored at −20°C or lower until shipment to the drug concentration measurement laboratory. The start and end dates/times of urine collection and the urine volume will be recorded in the CRF.

9.1.3 Shipment of Specimens

The collected specimens will be submitted on dry ice to the drug concentration measurement laboratory.

9.1.4 Measurement of Drug Concentrations

At the drug concentration measurement laboratory, the DS-1040a concentration in the received plasma and urine specimens will be measured by the liquid chromatography-tandem mass spectrometry method (lower limits of quantitation for plasma and urine specimens: 0.500 ng/mL and 10 ng/mL, respectively).

9.2 Pharmacodynamic Endpoints

As pharmacodynamic endpoints, fibrinolytic biomarkers (D-dimer level, activity of the target molecule of TAFIa, TAFI antigen level, and changes in coagulation and fibrinolytic parameters in the fibrin clot structure) will be measured. The TAFI antigen level will be determined using specimens collected at the following 3 time points: before study drug administration and at 6 hours (5 minutes) and 24 hours (±10 minutes) after the start of study drug administration. For the other endpoints, specimens collected at the following 4 time points will be used: before study drug administration and at 6 hours (−5 minutes), 24 hours (±10 minutes), and 48 hours (±15 minutes) after the start of study drug administration.

9.2.1 Collection of Plasma Specimens

Blood collection time points: Before the start of study drug administration and at 6 (−5 minutes), 24 (±10 minutes), and 48 (±15 minutes) hours after the start of study drug administration
A total of 4 time points

Blood collection volume: 9 mL/collection

Using a vacuum blood collection tube (with 3.2% sodium citrate), venous blood will be collected. Each tube will be mixed by inversion immediately after blood collection. The tube will then be centrifuged promptly at room temperature and 1500 × g for 15 minutes. The separated plasma will swiftly be aliquoted into eight storage vials and stored at −70°C or lower until shipment to the drug concentration measurement laboratory. The investigator or subinvestigator will record the date/time of blood collection in the CRF.

The procedures for the handling of specimens are detailed in the separately prepared "Procedures for Handling of Specimens for Pharmacodynamic Analysis."

9.3 Pharmacogenomic Analysis

9.3.1 Long-term Preservation of the Specimens for Genomic or Genetic Analysis (Banking)

In preparation for a future case of obtaining new genomic or genetic information related to (pharmacokinetic/pharmacodynamic) response to DS-1040b or of performing genomic or genetic analysis to identify the cause of any serious adverse drug reactions observed in clinical studies, DNA specimens extracted from subjects' blood according to the procedures described below will be stored for a long period of time (ie, banking). A research protocol will be newly prepared when specific details of genomic or genetic analysis are determined.

The procedures for the handling of specimens will be detailed in the separately prepared "Procedures for Banking."

9.3.1.1 Study Subjects for Banking

At the study centers approved for gene banking, an explanation of gene banking will be provided. Specimens will be collected from subjects who have given informed consent for such use (or whose legally acceptable representative has given informed consent for subject participation). For the subjects who give informed consent for gene banking, the investigator and subinvestigator will record the date of that consent in the CRF. If the subject has a medical history, etc., that might affect genomic or genetic information (for example, a history of allogeneic bone marrow transplant), that information will be entered in the CRF.

9.3.1.2 Collection of Specimens (Blood Collection) for Banking

During the subject's stay at the study site, after administration of DS-1040b, 5 mL of venous blood will be collected from a cutaneous vein of the forearm. The collected whole blood specimens will be stored frozen (temperature set at −20°C or below) until they are retrieved. The investigator or subinvestigator will enter the date of blood sampling in the CRF. The specimens will be assigned a code that is unrelated to the subject, so that no personal information about individual subjects will be revealed.

9.3.1.3 Storage Period

Banking specimens will be stored for a maximum of 20 years after the submission date of the protocol notification for this clinical study.

9.3.1.4 Disclosure of the Results of Genomic or Genetic Analysis Using Banked Specimens

The timing, methods, accuracy, and clinical significance of the genomic or genetic analysis using banked specimens are currently unknown. The sponsor will not disclose the results of genomic or genetic analysis to subjects or investigators.

9.3.1.5 Disposal of the Banked Specimens

At the end of the storage period, or during the storage period if the subject (or his/her legally acceptable representative) withdraws consent, the banked specimens will be promptly disposed of. However, the data will not be discarded if genetic analysis has been completed before the end of the storage period or before the subject withdraws consent for genetic analysis.

10. SAFETY EVALUATION AND REPORTING

10.1 Adverse Event Collection and Reporting

All clinical AEs (see Section 10.4.1 for definitions) occurring after the subject signs the ICF and up to the observation at Visit 6, whether observed by the investigator or subinvestigator or reported by the subject, will be recorded on the Adverse Event CRF page.

All AEs, SAEs, and events of special interest are to be reported according to the procedures in Section 10.5.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the investigator or subinvestigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings should be reported as AEs if they are symptomatic, lead to study drug discontinuation, require corrective treatment, or constitute an AE in the investigator's or subinvestigator's clinical judgment.

At each visit, the investigator or subinvestigator will determine whether any AEs have occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator or subinvestigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.4. The investigator's or subinvestigator's assessment must be clearly documented in the center's source documentation with the investigator's or subinvestigator's signature. At Visits 5 and 6, it is acceptable to collect AEs via telephone, etc.

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

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 10.4.2 for Definitions).

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

Any serious, untoward events that may occur subsequent to the reporting period that

the investigator or subinvestigator assesses as related to the study drug should also be reported as an SAE.

If any AE has occurred, the investigator or subinvestigator will take appropriate actions, notify the sponsor, and continue follow-up until the subject recovers to the pre-event condition with resolution or relief of the AE as far as possible. However, even if the AE is not confirmed to have resolved or relieved, if it is judged that the subject's condition remains stable and the safety can be assured, the investigator or subinvestigator will explain the matter to the subject, and the follow-up of the study will be completed.

10.2 Safety Endpoints

Not applicable.

10.3 Adverse Events of Special Interest

10.3.1 Combined Elevations of Aminotransferases and Bilirubin

Combined elevations of aminotransferases and bilirubin, either serious or non-serious, and independent of causal relationship, meeting the laboratory criteria for a potential case of Hy's Law (ALT or AST >= 3 times the upper limit of normal [ULN] with simultaneous TBL >= 2 times the ULN) should always be reported to the sponsor using the CRF, with the investigator's or subinvestigator's assessment of seriousness, causality, and a detailed narrative. These events should be reported within 24 hours of the investigator or subinvestigator becoming aware of the event (for the procedures for reporting, refer to Section 10.5).

If the subject discontinues study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations as described in "Section 5.7 Subject Withdrawal/Discontinuation" in order to determine the nature and severity of the potential liver injury.

10.4 Adverse Event

10.4.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a subject, and does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994). In this study, AEs occurring during the period after informed consent and until Visit 6 (Day

90) will be recorded in the CRF. It should also be reported whether each event is associated with obvious bleeding or not.

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

10.4.2 Serious Adverse Event

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

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

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

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

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

10.4.3 Severity Assessment

The following definitions should be used to assess intensity of AEs:

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

- Severe: Incapacitating with inability to work or do usual activity, ie, interferes significantly with subject's usual function.

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

10.4.4 Causality Assessment

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

Related:

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

  or

- The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.

Not Related:

- The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

10.4.5 Action Taken Regarding Study Drug(s)

The investigator or subinvestigator will record the status of study drug administration (continued or discontinued) in the CRF.

10.4.6 Other Action Taken for Event

None.

- No treatment was required.

Medication required.

- Prescription and/or OTC medication was required to treat the AE.

Hospitalization or prolongation of hospitalization required.

- Hospitalization was required or prolonged due to the AE, whether or not medication was required.

Other.

10.4.7 Adverse Event Outcome

Recovered/Resolved

- The subject fully recovered from the AE with no residual effect observed.

Recovering/Resolving

- The AE improved but has not fully resolved.

Not Recovered/Not Resolved

- The AE itself is still present and observable.

Recovered/Resolved with Sequelae

- The residual effects of the AE are still present and observable.
- Include sequelae/residual effects.

Fatal

- Fatal should be used when death is a direct outcome of the AE.

Unknown

10.4.8 Assessment of Bleeding Adverse Events

The investigator or subinvestigator will determine whether each AE is a bleeding event, and will record it, with the presence or absence of external factors (with details, if present), in the CRF.

- In case of intracranial hemorrhage

  The type of intracranial hemorrhage (symptomatic or asymptomatic), the date/time of the NIHSS assessment (at baseline and onset), and the details of the event will be recorded in the CRF.

- In case of non-intracranial hemorrhage

  The presence or absence of a 5 g/dL or greater decrease in hemoglobin, the presence or absence of blood transfusion (with the date/time, name, amount of blood transfusion, and AE(s) requiring blood transfusion, if present), the presence or absence of surgical treatment (with details, if present), and the details of the event will be recorded in the CRF.

The final classification and assessment of bleeding events will be performed by the central adjudication committee member in a blinded fashion. The investigator or

subinvestigator will provide the sponsor with head imaging results used as the basis for assessment.

10.5 Serious Adverse Events and Adverse Event of Special Interest Reporting–Procedure For the Investigator or Subinvestigator

All AEs, SAEs, and events of special interest, will be reported in the CRF.

The investigator will report the occurrence of an SAE using the "Serious Adverse Event Report (for Clinical Studies of Drugs)" (Form 12-1/12-2) within 24 hours after becoming aware of the occurrence. The investigator will also submit a written report with details on the SAE to the sponsor and the head of the study center without delay. The written report to the head of the study center will be made in accordance with the procedure and format specified by the study center.

Combined elevations of aminotransferases and bilirubin, which is non-serious but meets the laboratory criteria for a potential case of Hy's Law [ALT or AST >= 3 times the ULN with simultaneous TBL >= 2 times the ULN] should always be reported to the sponsor using a format provided by the sponsor, within 24 hours of the investigator becoming aware of the event.

All events (serious and non-serious) must be reported with the investigator's or subinvestigator's assessment of the event's seriousness, severity, and causality to the 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 (including medical reports) will be retained at the study center and should not be submitted to the sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

See Section 16.11 for contact information for SAE reporting. If there are any questions related to the reporting of SAEs, contact will be made to the emergency address or the clinical research associate in charge.

10.6 Notifying Regulatory Authorities, Investigator, and Institutional Review Board/Ethics Committee

The sponsor will inform the investigator, institutional review board (IRB)/ethics

committee (EC), and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring at other study centers or in other studies of the same investigational drug.

10.7 Exposure In Utero During Clinical Studies

The sponsor must be notified of any female subject or male subject's female partner who becomes pregnant while receiving the study drug or within 90 days of discontinuing the study drug.

Although pregnancy is not technically an AE, 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 subinvestigator, to report pregnancy in any female subject or male subject's female partner using the "Pregnancy Outcome Follow-up Form" (Form J05-61). The investigator or subinvestigator should contact the clinical research associate to receive the "Pregnancy Outcome Follow-up Form" upon learning of a pregnancy. The investigator or subinvestigator should make every effort to follow the subject or the subject's female partner until completion of the pregnancy and complete the "Pregnancy Outcome Follow-up Form" with complete pregnancy outcome information, including normal delivery and induced abortion. The pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs outlined in Section 10.5.

10.8 Clinical Laboratory Evaluations

Not applicable.

10.9 Vital Signs

Not applicable.

10.10 Electrocardiograms

Not applicable.

10.11 Physical Findings

Not applicable.

11. OTHER ASSESSMENTS

Not applicable.

12. STATISTICAL METHODS

12.1 General Statistical Considerations

Statistical and pharmacokinetics analyses are summarized. For more specific analysis methods, a statistical analysis plan will be separately prepared.

12.2 Analysis Sets

Regarding the procedures for the selection of subjects and data to be included in analyses, the selection criteria will be defined prior to the start of study drug administration to the first subject in principle. Subjects and data will be extracted and identified according to these criteria, and exclusion flags for these data will be prepared.

During the procedures for the selection of subjects to be included in analyses, subjects to be excluded from each analysis set will be identified based on the definition of the analysis set. Subjects to be excluded will be identified using locked data (including data with protocol violations and data exclusion flags). Subject exclusion flags will be prepared and documented.

During the procedures for the selection of data to be included in analyses, data considered inappropriate for the use in analyses due to medical or other reasons will be identified. The selection criteria will be defined in the planned procedures for the selection of data, regardless of the reason for exclusion, and data to be excluded will be extracted and identified. Exclusion flags will be prepared for data identified to be excluded before data lock.

12.2.1 Safety Analysis Set

The safety analysis set is defined as the population consisting of subjects who are enrolled in the study, excluding "those who have not received the study drug."

12.2.2 Efficacy Analysis Set

The full analysis set (FAS) is defined as the population consisting of subjects who are enrolled in the study, excluding the following subjects:

1) Subjects who have not received the study drug
2) Subjects who have not undergone efficacy evaluation even once

12.2.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set is defined as the population consisting of subjects who are enrolled in the study and have received the investigational drug and also meet all of the criteria listed below. However, subjects receiving placebo will be excluded:

1) Receiving the investigational drug as specified in the protocol

2) Having no major protocol violations (eg, violation of the inclusion/exclusion criteria)
3) Having plasma drug concentration data collected and available for at least 1 time point

12.2.4 Pharmacodynamic Analysis Set

The pharmacodynamic analysis set is defined as the population consisting of subjects who are enrolled in the study and meet all of the following criteria:

1) Receiving the investigational drug as specified in the protocol
2) Having no major protocol violation (eg, violation of the inclusion/exclusion criteria)
3) Having pharmacodynamic data collected and available for at least 1 time point

12.3 Statistical Analysis

12.3.1 Efficacy Analyses

12.3.1.1 Primary Efficacy Analyses

1) Summary statistics of the NIHSS score at each assessment point will be calculated by treatment group. Summary statistics of the change in the NIHSS score at each assessment point relative to baseline will be calculated by treatment group.
2) The frequency of the mRS score at each assessment point will be tabulated by treatment group. The proportion of subjects with good prognosis based on the mRS score (mRS score of 0 to 2) on Days 30 and 90 will be calculated by treatment group.

12.3.1.2 Secondary Efficacy Analyses

Not applicable.

12.3.1.3 Exploratory Efficacy Analyses

The frequency of the TICI grade will be tabulated by treatment group.

In addition, the proportion of subjects achieving TICI 3 immediately after thrombectomy device treatment will be calculated by treatment group.

12.3.2 Pharmacokinetic/Pharmacodynamic Analyses

12.3.2.1 Pharmacokinetic Analyses

Summary statistics of plasma concentrations and pharmacokinetic parameters will be calculated by treatment group. In addition, changes in plasma concentrations over time will be graphically displayed.

Results of modeling and simulation (M&S), including population pharmacokinetics and pharmacokinetic/pharmacodynamic analyses, if performed, will be separately reported.

12.3.2.2 Pharmacodynamic Analyses

Summary statistics of pharmacodynamics parameters (D-dimer level, TAFIa activity, and TAFI antigen level) will be calculated by treatment group. In addition, changes in each pharmacodynamic parameter over time will be graphically displayed.

12.3.2.3 Biomarker Analyses

Not applicable.

12.3.2.4 Pharmacogenomic Analyses

Not applicable.

12.3.3 Safety Analyses

12.3.3.1 Analysis of Primary Endpoints

The point estimate and 95% confidence interval of each endpoint listed below will be estimated. Data from the placebo groups of all cohorts will be integrated, whereas data from the DS-1040b groups will be summarized by dose.

1) Incidence of symptomatic intracranial hemorrhage (defined by ECASS) within 36 hours after the start of study drug administration
2) Incidence of asymptomatic intracranial hemorrhage within 36 hours after the start of study drug administration
3) Incidence of non-intracranial (TIMI) major bleeding within 96 hours after the start of study drug administration

12.3.3.2 Adverse Event Analyses

The incidence of treatment-emergent adverse events (TEAEs) will be calculated by treatment group, and the frequency of each TEAE will be tabulated by event and by severity. Similar analyses will be performed for treatment-related and bleeding TEAEs.

A TEAE is defined as an AE that is not present prior to the study and occurs after the start of study drug administration but before Visit 5 (Day 30), or an AE that worsens in severity after the start of study drug administration but before Visit 5 (Day 30).

12.3.3.3 Clinical Laboratory Evaluation Analyses

Shift tables for the determination of normal and abnormal values will be prepared.

Summary statistics of hematology and blood chemistry data at each time point will be calculated by treatment group, and the change at each time point from baseline will be graphically displayed.

12.3.3.4 Vital Sign Analyses

Summary statistics of vital sign data at each time point will be calculated by treatment group, and the change at each time point from baseline will be graphically displayed.

12.3.3.5 Electrocardiogram Analyses

A frequency table of investigator-assessed 12-lead ECG data at each measurement point will be prepared.

12.3.3.6 Analysis of Physical Findings

Not applicable.

12.3.3.7 Exploratory Safety Analyses

Not applicable.

12.4 Proceeding to the Next Cohort

12.4.1 Procedures for Proceeding to the Next Cohort

In each cohort, subjects will be evaluated one by one to confirm the absence of symptomatic intracranial hemorrhage through Visit 2 (36 hours after study drug administration) before enrolling the next subject, until 3 subjects aged ≥ 81 years are enrolled in the DS-1040b group. The next subject will then be enrolled. The next subject cannot be enrolled until the absence of symptomatic intracranial hemorrhage for 36 hours after study drug administration is confirmed.

Assessment for proceeding to the next cohort will be performed according to the procedures specified below. Study drug administration for the next cohort will be initiated immediately after the decision on proceeding to that cohort is made; it is not necessary to have a certain interval between the cohorts.

1) The investigator or subinvestigator will review the safety data after Visit 4 assessment, and immediately prepare the CRF.
2) The sponsor will obtain the data for safety data review. The central adjudication committee member will assess intracranial hemorrhage and (TIMI) major bleeding in a blinded fashion.

3) Based on the available information, the sponsor will discuss with the medical expert to determine whether the study should proceed to the next cohort in reference to Section 12.4.2 "Criteria for Discontinuation or Temporary Discontinuation of the Study."

12.4.2 Criteria for Discontinuation or Temporary Discontinuation of the Study

If any of the criteria specified below are met, the study will be discontinued or temporarily discontinued. Similarly, the study may be discontinued or temporarily discontinued according to these criteria until 3 subjects aged ≥ 81 years are enrolled in the DS-1040b group in each cohort.

1) If the criterion below is met, the study will be discontinued at that point. After the decision on discontinuation is made, the sponsor will discontinue the study according to the procedures described in Section 16.9:
   - Occurrence of two events of symptomatic intracranial hemorrhage (intracranial hemorrhage with clinical deterioration causing an increase in the NIHSS score of >= 4 points [defined by ECASS]) not attributable to external factors at 36 hours after the start of DS-1040b administration in the DS-1040b group in one cohort
2) To ensure the safety of subjects, subject enrollment will be temporarily discontinued and the necessary actions to be taken, including discontinuation of the study, will be considered if any of the criteria listed below are met. If the study is continued based on the results of consideration, subject enrollment will be resumed. If the study is discontinued, the sponsor will discontinue the study according to the procedures described in Section 16.9:
   - Occurrence of one event of symptomatic intracranial hemorrhage (intracranial hemorrhage with clinical deterioration causing an increase in the NIHSS score of >= 4 points [defined by ECASS]) not attributable to external factors at 96 hours after the start of study drug administration (Visit 4) in the DS-1040b group in one cohort
   - Occurrence of one event of non-intracranial (TIMI) major bleeding at 96 hours after the start of study drug administration (Visit 4) in the DS-1040b group in one cohort
   - Occurrence of any events requiring the consideration of study discontinuation, such as severe hepatic impairment (eg, total bilirubin >= 10 mg/dL, AST or ALT >= 500 IU/L, ALP of 5 times the study center's reference range, bleeding tendency, symptoms of hepatic failure, including consciousness disorder [fulminant hepatitis], hepatic cirrhosis, hepatic tumor, jaundice persisting for

>= 6 months), severe renal impairment (BUN >= 40 mg/dL, creatinine >= 4 mg/dL, urine protein > 3+, macroscopic hematuria, blood clots, serum potassium >= 5.5 mEq/L), and treatment-related SAEs

The investigator or subinvestigator will retain the original copies of all source documents supportive of information recorded in the CRF. These original copies should be available at any time for review.

12.4.3 Criteria

12.4.4 Data Monitoring Committee

No data monitoring committee will be established in this study.

12.5 Sample Size Determination

Each cohort: 6 or 12 subjects for the DS-1040b group in the 0.6 mg cohort
16 subjects each for the 1.2, 2.4, and 4.8 mg cohort (12 and 4 subjects in the DS-1040b and placebo groups, respectively)

Total: 54 or 60 subjects

<Rationale>

The sample size in each cohort (6 or 12 subjects in each DS-1040b group) and the study discontinuation criterion (occurrence of two events of symptomatic intracranial hemorrhage [defined by ECASS] in the DS-1040b group in one cohort) were selected in reference to Study DS1040-A-U103, which is ongoing in Europe and the United States, to confirm the safety and tolerability of DS-1040b monotherapy in patients with acute ischemic stroke. The sample size for Study DS1040-A-U103 was determined based on the results of clinical studies of rt-PA therapy.[11,12] Based on the 16% incidence of symptomatic intracranial hemorrhage in these clinical studies of rt-PA therapy, a sample size that allows the assessment of an incidence of symptomatic intracranial hemorrhage of <= 16% (16 subjects per cohort) and the criterion for proceeding to the next cohort (occurrence of two events of symptomatic intracranial hemorrhage [defined by ECASS] in the DS-1040b group in one cohort) were selected in Study DS1040-A-U103.

In the 0.6 mg cohort, the safety in 6 or 12 subjects in the DS-1040b group will be confirmed. If DS-1040b at this dose is shown to be safe, the study will proceed to the next cohort.

12.6 Statistical Analysis Process

The clinical study will be analyzed by the sponsor or a designee/contract research organization (CRO).

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

All statistical analyses will be performed using SAS® Version 9.2 or higher (SAS Institute, Cary, NC 27513).

13. DATA INTEGRITY AND QUALITY ASSURANCE

The head of the study center and the investigator will provide direct access to all study-related documents, including source documents, at the implementation of monitoring and auditing by the sponsor as well as inspections by regulatory authorities and the IRB. The sponsor will have direct access to all study-related documents, including source documents, at the study center when performing monitoring and auditing to ensure appropriate implementation of the study and the reliability of the data. The sponsor will confer with the investigator in advance regarding procedures for source document verification.

13.1 Monitoring and Inspections

The sponsor's and CRO's clinical research associates and the regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, CRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and local regulations on the conduct of clinical research will be accomplished through the combination of onsite visits by the clinical research associate and remote review of study data. The frequency of the monitoring visit will vary based on the study progress at each study center. The clinical research associate is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The clinical research associate should have access to subject medical records and other study related records needed to verify the entries on the CRFs. Detailed information is provided in the monitoring plan.

The clinical research associate will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the investigator and will ensure that appropriate action (s) designed to prevent recurrence of the detected deviations is taken and documented.

The investigator agrees to cooperate with the clinical research associate to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the sponsor and documented.

In accordance with ICH GCP and the sponsor's audit plans, this study site may be selected for audit by representatives from the sponsor. Audit of study center facilities (eg, pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings. In the event that a regulatory authority informs the investigator that it intends to conduct

an inspection, the sponsor must be notified immediately.

13.2 Data Collection

13.2.1 Preparation of the Case Report Form

A CRF must be completed by the investigator or subinvestigator for each subject who signs an ICF and undergoes any screening procedure. If a subject is not treated, the reason must be recorded on the CRF. All data collected during the study must be recorded in this individual, subject-specific CRF. Instructions will be provided for the completion of the CRF and any corrections made will be automatically documented via the electronic data capturing (EDC) software's "audit trail."

13.2.2 Precautions for Entering Data in the Case Report Form

The CRF (completed by the investigator), the Central Adjudication Form (prepared by the central adjudication committee member), the Drug Concentration Assay Data Report (prepared by the laboratory performing drug concentration assays), the Blood Coagulation Data Report (prepared by the laboratory performing blood coagulation assays), and the Biomarker Data Report (prepared by the laboratory performing biomarker assays) will be prepared in the study.

In this study, the CRF will be recorded using the EDC system (EDC System, Table 13.2-1), which is designed to electronically prepare CRFs. The CRF (including an audit trail) will be prepared for each subject and the one that was signed by the investigator will be handled as the original. A validated EDC system will be used in the study.

Table 13.2-1 EDC System

EDC system name	Medidata Rave®
EDC system development corporation	Medidata Solutions, Inc.
How to enter data	Data entry via the web interface
Terminal for data entry	PC at the study center
OS prohibited	None
Browser	Medidata Rave® supports any browser that conforms to HTML 5 and CSS2. JavaScript needs to be enabled in the browser.
Recommended screen resolution	1024 × 764 resolution or higher
Recommended connection speed	128 kbps or higher
Others	Adobe Flash Player ver. 10 or higher

13.3 Data Management

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

To ensure the quality of clinical data across all subjects and study centers, subject data will be reviewed according to the specifications given to the sponsor. Data will be vetted both electronically and manually for CRFs and subject data will be checked for consistency, completeness and any apparent discrepancies. CRF data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated as queries within the EDC application.

Data received from external sources such as the central laboratory will be reconciled to the clinical database in accordance with the data management plan.

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

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

13.4 Study Documentation and Storage

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

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

The investigator will be expected to maintain an Enrollment Log of all subjects enrolled in the study including their assigned study number.

The investigator will maintain a confidential subject number list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the investigator to reveal the identity of any subject when necessary.

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

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed 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 study center (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study center policy. Prior to

transfer or destruction of these records, the sponsor must be notified in writing and be given the opportunity to further store such records.

If the items listed below are directly entered in the CRF (specifically, if there are no documents or electronically recorded data before the entries are made), the entries in the CRF will be regarded as the source data.

(1) Directly entered data on each item (eg, entries in the comment section)
(2) Entries "None" or "Not done" for each item
(3) Reason for use of the concomitant drugs and therapies
(4) The severity, seriousness, date of outcome, and causality with the study drug of AEs
(5) Reason for withdrawal

13.5 Record Keeping

The head of the study center and the person responsible for record keeping 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 of the sponsor and/or applicable regulatory authorities. Essential documents contained in the Trial Master File include:

- Subject files: CRFs (copies), ICFs, and supporting copies of source documentation (if kept).
- Study files: the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the EC/IRB and the sponsor.
- Study drug-related records: records of receipt of the study drug supplies at the study center, records of study drug storage and management at the study center, Study Drug Return Form and Study Drug Storage/Accountability Log (copy), and other correspondence.

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

All study related essential documentation will be retained by the head of the study center and the person responsible for record keeping until at least 3 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have lapsed since the formal discontinuation of clinical development of the investigational drug. 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/study center as to when these documents no longer need to be retained.

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

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

Regarding the long-term storage (banking) of specimens for genome/gene analysis, the study center should store the subject screening list for a maximum of up to 20 years after the end of the clinical study to meet a subject's request for withdrawal of consent after the end of the clinical study.

14. FINANCING AND INSURANCE

14.1 Finances

Prior to starting the study, the study center will sign a clinical study agreement with the sponsor. This agreement will include the financial information agreed upon by the parties.

14.2 Reimbursement, Indemnity, and Insurance

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

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

15. PUBLICATION POLICY

[redacted]

16. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

16.1 Compliance Statement, Ethics, and Regulatory Compliance

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

- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 Mar 1997 and/or;
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 of 25 Nov 2014;

The genome/gene analysis to be performed during the study, banking of clinical specimens for the genome/gene analysis and a research study using the specimens will be performed in accordance with the "Ethical Guidelines for Human Genome/Gene Analysis Research" and "Ethical Guidelines for Medical and Health Research Involving Human Subjects" in addition to the above-mentioned regulations (applicable only to the study center[s] where the conduct of gene banking research is approved).

16.2 Subject Confidentiality

The investigator, subinvestigator, and the sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP.

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

In compliance with ICH GCP Guidelines, it is required that the investigator and study center permit authorized representatives of the company, of the regulatory authorities, and the 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.

16.3 Informed Consent

The investigator or subinvestigator will explain the details of the study listed below to subject candidates (or their legally acceptable representatives who can look after the best interest of the subjects) in a readily understandable way using the informed consent

documents, and will obtain written informed consent to participate in the study from the subjects by their own free will. Before obtaining consent, the investigator or subinvestigator should give the subjects (or their legally acceptable representatives) adequate time and opportunity to ask questions to decide whether to participate in the study, and should answer the questions to the satisfaction of the subjects.

The investigator or subinvestigator who has provided an explanation and the subject (or his/her legally acceptable representative) who has given consent will sign and date the consent form. If a legally acceptable representative signs the ICF, his/her relationship with the subject should be provided in the ICF. If study staff have provided a supplementary explanation to the subject (or his/her legally acceptable representative), the study staff should also sign and date the form. A copy of the consent form along with the subject information form will be provided to the subject (or his/her legally acceptable representative), and the original consent form will be retained at the study center. The investigator or subinvestigator will document (eg, in the original consent form or medical record) that a copy of the consent form and subject information form have been provided to the subject (or his/her legally acceptable representative).

After obtaining consent from the subject, the investigator, subinvestigator, or study staff will enter the subject's date of birth, sex, and the date of informed consent into the IRT system.

[Items to be explained to the subjects]

1) That the study involves research
2) Study objectives
3) Study methods (including experimental aspect of the study, inclusion criteria for subjects and, if subjects are randomized to treatment arms, the probability of randomization to each treatment)
4) Planned duration of participation in the study
5) Planned number of subjects in the study
6) Foreseeable physical and mental benefits (or, if no such benefit, a statement to that effect) and risks associated with study treatment
7) Presence or absence of other treatment methods and expected important benefits and risks of the methods
8) Compensation and treatment that the subject can receive if any study-related injury occurs as a result of participation in the study
9) Statements that participation in the study is based on the subject's own free will; that the subject can refuse to participate in, or withdraw from, the study at any time; that he/she will not be disadvantaged even if he/she refuses to participate in or withdraw from the study; and that he/she will not lose any benefits that would

have been given, even if he/she does not participate in the study

10) A statement that the subject or his/her legally acceptable representative will be promptly informed if any information that may affect the subject's (or his/her legally acceptable representative's) willingness to continue participation in the study is obtained
11) Conditions or reasons for withdrawal from the study
12) Statements that the clinical research associates, responsible auditors, IRB, and regulatory authorities can access source documents; that in such a case, the subject's privacy will be protected; and that the subject is deemed to have consented to such access by writing his/her name and affixing his/her seal on or signing the consent form
13) A statement that the subject's privacy will be protected even if the results of the study are published
14) Details of expenses the subject needs to pay, if any
15) Details of payment to the subject, if any
16) Name, title, and contact information of the investigator or subinvestigator
17) Contact information of the study center in the event that the subject requires further information regarding the study or the rights of subjects, or in the event of study-related injury
18) Responsibilities of subjects
19) The type of IRB that evaluates and reviews the appropriateness of the study, etc., items to be evaluated and reviewed by the IRB, and other matters regarding the IRB in relation to the study

16.4 Informed Consent for the Gene Banking Research

The investigator or subinvestigator of the study centers where long-term storage (banking) of clinical specimens for the genome/gene analysis to be performed at an unspecified time is allowed, will explain the matters listed below to subjects or their legally acceptable representatives providing consent for the core clinical study in a readily understandable way and obtain written informed consent for the banking separately from the consent provided for participation in the core study, by their own free will. The consent must be obtained before specimen collection.

1) Characteristics and properties of genetic information
2) Research objectives
3) Research methods
4) Expected benefits for physical and mental health of the subject and possible risks to the subject participating in the research

5) Statements that participation in the pharmacogenomics study is based on the subject's own free will and that the subject can refuse to participate in, or withdraw from, the study at any time; that he/she will not be disadvantaged even if he/she withdraws his/her consent; and that participation in the core clinical study will not be affected by refusal to participate in the pharmacogenomics study.
6) Handling of specimens and data after withdrawal of consent
7) Matters on the method of handling, duration of storage, and disposal of specimens
8) Compensation that the subject can receive
9) Disclosure of study results and to whom the results belong
10) Details of expenses the subject needs to pay, if any
11) A statement that no payment is made for specimens provided by the subject
12) Protection of human rights, including the subject's privacy

16.5 Regulatory Compliance

Prior to the start of the study, it must be reviewed and approved by the IRB specified in Section 27 of the GCP ordinance. During the course of the study, the appropriateness of study continuation will be reviewed annually, or more frequently upon the IRB's request. The appropriateness of study continuation will also be reviewed if any information that may affect the safety of subjects or the conduct of the study is obtained.

16.6 Protocol Deviations

The investigator should conduct the study in compliance with the protocol agreed to by sponsor and, if required, by the regulatory authority(ies), and which was given approval by the IRBs.

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 subinvestigator should document and explain any deviation from the approved protocol.

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

16.7 Supply of New Information Affecting the Conduct of the Study

If any information that may affect the subject's (or his/her legally acceptable representative's) willingness to continue participation in the study is obtained, the investigator or subinvestigator will promptly inform the subject (or his/her legally

acceptable representative) and confirm the subject's (or his/her legally acceptable representative's) willingness to continue participation in the study. The investigator or subinvestigator will also document (eg, in the medical record) the date of explanation, the person who has given the explanation, the details of the explanation, the subject's (or his/her legally acceptable representative's) decision, and the date of confirmation. The investigator will also promptly revise the consent form and subject information form, as necessary, and submit them to the sponsor. The investigator will also report the revised forms to the head of the study center and request review and approval by the IRB. The informed consent process for a new subject should not be started before IRB approval has been obtained. For subjects who are already participating in the study, their consent to remain in the study should be obtained in the same manner as the above-mentioned informed consent procedure using the revised consent form and subject information form. A copy of the said consent form and subject information form will be provided to the subject or his/her legally acceptable representative. The investigator or subinvestigator will document (eg, in the original consent form or medical record) that a copy of the consent form and subject information form have been provided to the subject (or his/her legally acceptable representative).

16.8 Protocol Amendments

If any amendment has to be made to the clinical study protocol after the start of the study, the sponsor will examine the appropriateness of the amendment and potential influences on the evaluations in the study, and after discussion with the medical expert, etc., if necessary, determine whether to make the amendment or not. The sponsor will clearly document and retain the content of the discussion, the presence or absence of the amendment, and the reason, etc.

The sponsor will promptly notify the investigator of the specific details of the amendment to the protocol. If the protocol is updated to a new version, the sponsor will newly obtain written agreement of the investigator and implement the procedures specified by the study center.

16.9 Study Termination

The sponsor will discuss events meeting any of the following criteria with the medical expert as appropriate to determine whether the study should be discontinued:

1) If any new safety information regarding the study drug, or information regarding SAEs is obtained
2) If any major GCP violation or significant protocol deviation is committed by the sponsor, the study center, or the investigator

3) Combined elevations of aminotransferase and bilirubin meeting the laboratory criteria for a potential case of Hy's Law
4) If any other new information of such relevance is obtained during the study

If the sponsor decides to discontinue the study entirely after consultation with the medical expert, etc., including the case of deciding on study discontinuation according to the criteria shown in Section 12.4.2, the sponsor will promptly notify the head of the study center in writing with the reason for discontinuation. The head of the study center will promptly notify the investigator and the IRB in writing of the discontinuation and the reason for discontinuation.

If the study is discontinued permanently or temporarily for any reason, the investigator will promptly notify the subjects participating in the study of the fact, and take appropriate actions and perform the necessary tests to verify the safety of subjects.

16.10 Data and Safety Monitoring Board

A data and safety monitoring board will not be established in this study.

16.11 Address List

Refer to Appendix "Study Administrative Structure."

16.11.1 Emergency Contact Information

1) Night hours (18:00 to 9:00) and Saturdays, Sundays, and holidays (all day):
Emergency contact number
PPD

2) Daytime (9:00 to 18:00) from Monday through Friday (except holidays):
PPD Clinical Development Department, R&D Division, Daiichi Sankyo Co., Ltd.
PPD PPD

17. REFERENCES

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14. Albers GW, Marks MP, Kemp S, et al. Thrombectmy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018, 378: 708-718.

18. APPENDICES

18.1 Schedule of Events

Table 18.1-1 Schedule of Events

Study Period		Screening Randomize	Treatment Period								Follow Up		Dis-continua-tion[g]
Visit		1						2	3	4	5	6	
Hour		Predose	0	0.5	3	6	18	24	48	96			
Day											30	90	-
Informed consent		○											
Baseline subject characteristics Inclusion/exclusion criteria		○											
Prior treatment and concomitant drugs		○						○	○	○			○
Physical examination		○						○	○	○	○[a]	○[a]	○
Height/body weight measurement		●[b]											
Head imaging (CT or MRI)		●						○[c]					○[h]
Neurological symptoms	NIHSS	●		○[d]				○[d]					○[h]
	mRS										○	○	
Vital signs		●						○	○	○			○
12-lead ECG		●						○					○[h]
Hematology and blood chemistry		●				○		○		○			○
aPTT, PT, INR		●				○		○					○[h]
PT, INR, aPTT, fibrinogen[i]		○				○		○		○			○
TAFIa activity, D-dimer level, fibrin clot structure[i]		○				○		○	○				○[h]
TAFI antigen level		○				○		○					○[h]
AE reporting		◄———	———	———	———	———	———	———	———	———►			○
Study drug administration			◄———	———	———	———	———►						
Cerebral artery revascularization			○[e]	Applicable also to repeated procedures									
Pharmacokinetics (blood)i		○		○	○	○	○	○	○	○			○
Pharmacokinetics (pooled urine)i			◄———	———	———	———	———	———►					○[h]
Gene banking			○[f]										

●: Data obtained prior to informed consent may be used.

a: Follow-up via telephone, etc., will also be acceptable.

b: Height and body weight will be measured before Visit 4.

c: Head imaging (CT or MRI) at Visit 2 will be performed within 24 hours to 36 hours after the start of study drug administration.

d: The NIHSS assessment will be performed before the start of study drug administration, immediately after thrombectomy device treatment, and at 24 ± 4 hours after the start of study drug administration.

e: Thrombectomy will in principle be performed after study drug administration.

f: Blood specimens for gene banking will be collected from subjects who have given informed consent at a single time point in the inpatient setting.

g: If the study is discontinued after Visit 4, the assessment at discontinuation is not required.

h: These events will take place only if the study is discontinued before 24 hours after the start of study drug administration (Visit 2).

i: The central laboratory will perform the assays.

Table 18.1-2 Allowable Time Window for Events

Visit	Time after Dosing (h)	Allowable Time Window	Events
1	0.5	−5 minutes	Pharmacokinetics
	3	±10 minutes	Pharmacokinetics
	6	−5 minutes	Hematology/blood chemistry, blood coagulation (local), blood coagulation (central), pharmacodynamics, pharmacokinetics
	18	±10 minutes	Pharmacokinetics
2	24	±12 hours	Physical examinations, vital signs, 12-lead ECG, hematology/blood chemistry, blood coagulation (local)
		+12 hours	Head imaging (CT or MRI)
		±4 hours	Neurological symptoms (NIHSS)
		±10 minutes	Blood coagulation (central), pharmacodynamics, pharmacokinetics
3	48	±12 hours	Physical examinations, vital signs
		±15 minutes	Pharmacodynamics, pharmacokinetics
4	96	±12 hours	Physical examinations, vital signs, hematology/blood chemistry
		±15 minutes	Blood coagulation (central), pharmacokinetics
5	-	Day 30±7 days	Neurological symptoms (mRS)
6	-	Day 90±7 days	Neurological symptoms (mRS)

18.2 Additional Information

18.2.1 GCP compliance

With regard to "related regulations" in Section 15.1 (for Japanese study centers only): This study will be conducted in compliance with the standards stipulated in Article 14-3 and Article 80-2 of the Pharmaceutical Affairs Law and by the "Ordinance Regarding Good Clinical Practice" (MHW Ordinance No. 28, dated 27 Mar 1997; GCP Ordinance). In compliance with the ethical principles of the Declaration of Helsinki, the human rights, welfare, and safety of the subjects will be the first considerations in the conducting of this study.

As for EDC, the study will be conducted in accordance with the "Use of Electromagnetic Records and Electronic Signature in Application for Approval or Permission, etc., of Medical Products, etc." (PFSB Notification No. 0401022).

18.2.2 Study Period

01 Apr 2017 to 30 Jun 2020

18.2.3 Payment for Participation, Compensation for Study-related Injuries, and Insurance

18.2.3.1 Payment for Participation

As compensation to reduce the subject's burden, etc., the study center will pay subjects an amount from the funds paid by the sponsor to the study center according to separately specified regulations of the study center.

18.2.3.2 Compensation for Study-related Injuries

If a subject incurs study-related injuries that are caused by participation in this clinical study, the investigator or subinvestigator will provide treatment or other required interventions. If a subject requests compensation or reparation for study-related injuries, this will be promptly communicated to the sponsor. The sponsor will establish a procedures manual for compensation in the event that a subject incurs study-related injuries, and will implement measures such as liability insurance coverage. The sponsor will be responsible for any of the subject's personal costs for treatment that occur because of the study-related injury and that are not otherwise covered by sources such as health insurance. If there is a claim for compensation for permanent disability, etc., the Relief System for Sufferers from Adverse Drug Reactions provides a useful guide for the awarding of compensation. The sponsor will not be liable for the injury if any of the following apply.

1) There is proof that the injury is definitely caused by some other factor.

2) There is no temporal relationship between administration of the study drug and the injury.
3) Another party is clearly at fault, such as in a traffic accident.
4) The subject failed to benefit from treatment because the drug did not demonstrate effectiveness or the subject took the placebo.
5) A subject or a subject's partner is found to be pregnant during the study.
6) For no justifiable reason, the subject failed to follow the protocol.

The compensation may be reduced or forfeited if the study-related injury is clearly due to deliberate misconduct or gross negligence on the part of the subject or the study center.

18.2.3.3 Insurance

The sponsor will arrange in advance for insurance to cover potential compensation for study-related injuries. The study center(s) will take measures in advance, such as the purchase of insurance, to cover study-related injuries that are due to medical malpractice.

18.2.4 Notifying Any Other Physicians Treating Subjects of Their Study Participation

For subjects enrolled in the study who are receiving treatment by another physician, the investigator or subinvestigator must notify the physician, after obtaining permission from the subject, that the subject is participating in the study.

The investigator or subinvestigator will ask subjects who have provided informed consent whether they are being treated by another physician (eg, a physician in another department of the study center or at another medical institution) or not. If the subject is receiving treatment by another physician, the investigator or subinvestigator will inform the physician of the subject's participation in the study with the subject's approval and record the provision of this information in the medical record, etc.

18.2.5 Quality Control and Quality Assurance

The sponsor will implement quality assurance and a quality control system in accordance with the standard operating procedures specified by the sponsor to ensure that the conduct of the study and the generation, recording, and reporting of data are in compliance with the following:

1) The clinical study protocol
2) Standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and

Cosmetics (hereinafter, the PMD Act)

3) GCP Ordinance

The sponsor will also perform quality control at each stage of data handling to ensure the reliability and proper processing of all study-related data. The methods for quality control will be prepared in advance in accordance with the standard operating procedures specified by the sponsor, and the implementation will be recorded.

The sponsor's auditor will perform GCP auditing as part of quality assurance operations to determine whether the study is conducted in compliance with GCP, the clinical study protocol, and written procedures, etc. independently and separately from the regular monitoring and study quality control operations.

Study Administrative Structure (Appendix)

Sponsor	Daiichi Sankyo Co., Ltd. 3-5-1 Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan PPD
Clinical study director	PPD Clinical Development Department
Global Clinical Lead	PPD Global Cardiovascular and metabolic Therapeutic Area, Daiichi Sankyo Pharma Development 399 Thronall Street, Edison, NJ 08837 PPD
Clinical Study Lead	PPD Clinical Development Department 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan PPD
Clinical research associate (representative)	PPD Clinical Development Department
Person responsible for study drug management	PPD Clinical Supply Management Department
Person responsible for pharmacokinetic analysis	PPD Clinical Pharmacology Department
Person responsible for concentration measurement	PPD Clinical Pharmacology Department
Modeling & Simulation Approver	PPD Clinical Pharmacology Department
Sub-Functional Lead of Data Management	PPD Biostatistics & Data Management Department
Sub-Functional Lead of Biostatistics	PPD Biostatistics & Data Management Department
Person responsible for quality management	PPD Development Function
Person responsible for safety information measures	PPD Pharmacovigilance Department
Person responsible for safety information evaluation	PPD Pharmacovigilance Department 3-5-1 Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan PPD
Person responsible for genome/gene analysis	PPD Biomarker & Translational Research Department
Person responsible for banking of genetic analysis specimens	PPD Biomarker & Translational Research Department
Consultation contact on banking	Biomarker & Translational Research Department 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan PPD
Medical Expert	PPD PPD Kobe City Medical Center General Hospital 2-1-1 Minatojimaminamimachi, Chuo-ku, Kobe, Hyogo 650-0047, Japan PPD Duties: The medical expert will give advice on medical issues during planning and conduct of the study, and preparation of the clinical study report. The medical expert will affix his/her signature to the clinical study report if he/she is assessed to be appropriate as an authorizer of the report.
IRT vendor	PAREXEL Informatics PPD

	9F3, RBM East Yaesu Building, 2-9-1 Hatchobori, Chuo-ku, Tokyo 104-0032, Japan 13F, Kayaba-cho Tower, 1-21-2, Shinkawa, Chuo-ku, Tokyo Japan PPD Duties: The IRT vendor will perform duties related to subject enrollment and liaison with the study center and sponsor, according to the consignment contract.
EDC System Development	Medidata Solutions, Inc. PPD 350 Hudson Street, 9th Floor, New York, New York 10014, USA PPD Duties: The company will perform operation, management, and maintenance of the EDC system according to the consignment contract.
EDC System Support	Fujitsu Limited PPD TOKYU REIT Kamata Building, 5-13-2 Kamata, Ohta-ku, Tokyo 144-0052, Japan PPD Duties: The company will perform EDC system support activities according to the consignment contract.
Independent biostatistician	PPD Statistics and Product Support Services, Logistics Solutions, PAREXEL Informatics Castle Wharf, No. 4 Canal Street, Nottingham, NG1 7EH, United Kingdom PPD PPD Duties: The independent biostatistician will prepare a randomization schedule as instructed by the sponsor.
Study center and Investigator	PPD Kobe City Medical Center General Hospital Kobe City Hospital Organization 2-1-1 Minatojimaminamimachi, Chuo-ku, Kobe, Hyogo 650-0047, Japan PPD Duties: To agree on the protocol, the investigator will prepare and revise the ICF, select subjects and obtain their consent, instruct and supervise the subinvestigators and study staff, provide materials and information, cooperate with monitoring and auditing, report deviations of or changes from the protocol and AEs, complete the CRFs, and retain the "documents or records related to the clinical study" in consultation with the sponsor.
Central adjudication committee member	PPD Jichi Medical University, School of Medicine 3311-1 Yakushiji, Shimotsuke-shi, Tochigi-ken, 329-0498, Japan PPD Duties: The central adjudication committee member will classify and assess bleeding events based on image data and the CRF data provided by each study center.
Central Laboratory (PT, INR, aPTT, fibrinogen)	SRL Medisearch Inc. PPD

	Clinical Study Support Business Division Shinjuku I-Land-Tower 10F, 6-5-1, Nishishinjuku, Shinjuku-ku, Tokyo 163-1310, Japan PPD Duties: The central laboratory will temporarily store specimens for pharmacodynamic and pharmacokinetic assays provided by each study center according to the consignment contract. Using these specimens, the laboratory will perform PT, INR, aPTT, and fibrinogen assays and send the other specimens to another designated central laboratory.
Measurement of Drug Concentrations	Worldwide Clinical Trials Early Phase Services/Bioanalytical Sciences, Inc. PPD 8609 Cross Park Drive, Austin, Texas, 78754, USA PPD Duties: The facility will analyze and store specimens sent by each study center according to the consignment contract.
Central Laboratory (TAFIa activity, D-dimer level, TAFI antigen level)	Medpace Reference Laboratories PPD 5365 Medpace Way, Cincinnati, Ohio 45227, USA PPD Duties: The central laboratory will analyze and store specimens sent by each study center according to the consignment contract.
Central Laboratory (fibrin clot structure)	Diagnostica Stago, Inc. PPD 5 Century Drive, Parsippany, New Jersey, 07054, USA PPD Duties: The central laboratory will analyze and store specimens sent by each study center according to the consignment contract.
Contracted Organization for Storage and Management of Clinical Specimens for Genome/Gene Analysis	SRL Medisearch Inc. PPD Shinjuku I-Land-Tower 10F, 6-5-1, Nishishinjuku, Shinjuku-ku, Tokyo 163-1310, Japan PPD Duties: The organization will extract DNA from clinical specimens for genomic or genetic analysis (blood, etc.), store and manage specimens (banking), and disposal of the specimens according to the consignment contract.
Contract Research Organization	CMIC Co., Ltd. PPD Nakanoshima Central Tower, 2-2-7 Nakanoshima, Kita-ku, Osaka, 530-0005 Japan PPD Duties: The company will carry out monitoring activities according to the sponsor's standard operating procedure based on the consignment contract.
Department Responsible for Audit	PPD Quality & Safety Management Division, Daiichi Sankyo Co., Ltd. 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan PPD Duties: The department will perform GCP auditing.