Dose Finding Study of MCI-186 in Acute Ischemic Stroke

Clinical Protocol

Sponsor

Mitsubishi Tanabe Pharma Corporation

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This study shall be conducted in compliance with the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, the Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs, related laws and regulations, and the protocol.

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Separate sheets

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List of Abbreviations

Abbreviation	Full Description	Japanese translation (if available)
ADL	Activities of Daily Living	Activities of Daily Living
BI	Barthel Index	-
CRF	Case Report Form	case report form
DWI	Diffusion Weighted Image	Diffusion-weighted imaging
EDC	Electronic Data Capture	electronic data capture
eGFR	estimated Glomerular Filtration	estimated glomerular filtration rate
[redacted]	[redacted]	-
FAS	Full Analysis Set	Full Analysis Set
FIM	Functional Independence Measure	Functional Independence Measure
FLAIR	Fluid-attenuated Inversion Recovery	-
GCP	Good Clinical Practice	Good Clinical Practice
GMP	Good Manufacturing Practice	Good Manufacturing Practice
IRB	Institutional Review Board	Institutional Review Board
MRA	Magnetic Resonance Angiography	Magnetic resonance angiography
MRI	Magnetic Resonance Imaging	magnetic resonance imaging
mRS	modified Rankin Scale	-
NIHSS	National Institutes of Health Stroke Scale	-
PPS	Per Protocol Set	Per Protocol Set
PTA	Percutaneous Transluminal Angioplasty	percutaneous transluminal angioplasty
QALY	Quality-Adjusted Life Year	quality-adjusted life year
QST	Quantitative Sensory Test	Quantitative sensory testing
rt-PA	recombinant tissue-type Plasminogen Activator	recombinant tissue plasminogen activator
SUSAR	Suspected Unexpected Serious Adverse Reaction	-
TCD	Transcranial Doppler	transcranial Doppler
TIA	Transient Ischemic Attack	Transient ischaemic attack
T2*WI	T2*-Weighted Image	T2* -weighted images

Definitions of Terms

Term	Definition
MCI-186	Edaravone
Day1(D1)	Start date of investigational product treatment
12 weeks before informed consent	It is defined as the same day of the week 12 weeks prior to the informed consent date.
H group	Continuous IV high dose group
L group	Continuous IV low-dose group
Control	Approved dosage and administration group

Protocol Summary

1 Study Title

Dose Finding Study of MCI-186 in Acute Ischemic Stroke

2 Study Objectives

To evaluate the efficacy and safety of MCI-186 administered by bolus injection followed by 72 hours continuous intravenous infusion in patients with acute ischaemic stroke in a double-blind, parallel-group, comparative study of the approved dosage and administration of MCI-186 as a control.

3 Subjects

3.1 Subjects

Patients with acute ischaemic stroke within 24 hours after onset

3.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria at the time of enrollment.

(1) Patients who have provided appropriate written consent to participate in the study by themselves or their legally acceptable representatives

(2) Patients aged 20 to 85 years, inclusive, at the time of informed consent

(3) Patients who can start receiving investigational product within 24 hours after onset

(4) Patients with new ischemic areas confirmed by MRI only in the tentorium

(5) Patients with neurological symptoms defined as NIHSS ≥ 4 and ≤ 22

3.3 Exclusion Criteria

Patients who meet any of the following exclusion criteria at enrollment will be excluded from the study.

(1) Patients with a pre-existing disorder equivalent to mRS ≥ 2

(2) Patients being treated with antibiotics for infections at the time of enrollment

(3) Patients who have received or are scheduled to receive treatment with prohibited concomitant drugs (thrombolytics, etc.) or prohibited concomitant therapies (Endovascular treatment, surgical treatment, etc.) for primary disease

(4) Patients for whom the investigator (subinvestigator) judges that the efficacy endpoints (NIHSS, mRS, BI, etc.) set in this study cannot be appropriately evaluated. For example, patients in whom improvement of NIHSS ≥ 4 points cannot be expected due to neurological symptoms existing from before the onset of cerebral infarction, patients with Alzheimer's type dementia, patients with Parkinson's disease, etc.

(5) Patients with severe disturbance of consciousness (Japan Coma Scale ≥ 100)

(6) Patients who are clearly complicated with peripheral vascular disease or peripheral neuropathy and cannot undergo neurological examination in the investigator's (subinvestigator's) opinion

(7) Patients with severe renal disorder (e.g., eGFR < 30)

(8) Patients with severe hepatic disorder (Patients with ALT, AST, or γ-GTP exceeding 2.5 times the upper limit of normal, etc.)

(9) Platelet count < 100,000/mm ^{3}

(10) Patients diagnosed with a disease other than cerebral infarction (Intracranial hemorrhage, subarachnoid hemorrhage, arteriovenous malformation, moyamoya disease, brain tumor, etc.) or cerebral aneurysm with a maximum diameter of > 7 mm by MRI on admission

(11) Patients with a history or complication of drug abuse or alcohol dependence

(12) Patients with a history or complication of malignant tumor within 5 years after the onset of cerebral infarction

(13) Patients with a history of hypersensitivity to edaravone formulations

(14) Patients with a cardiac disease requiring inpatient treatment (e.g., acute myocardial infarction, cardiac failure), who have a problem in general condition, and who are judged by the investigator (subinvestigator) to be ineligible for treatment with this study

(15) Patients in whom MRI scan cannot be performed

(16) Male patients and female patients of childbearing potential who do not agree to use birth control from the day of informed consent to the day after the last dose of investigational product

(17) Patients who are pregnant, breastfeeding, or possibly pregnant

(18) Patients who have received any other investigational product within 12 weeks before informed consent

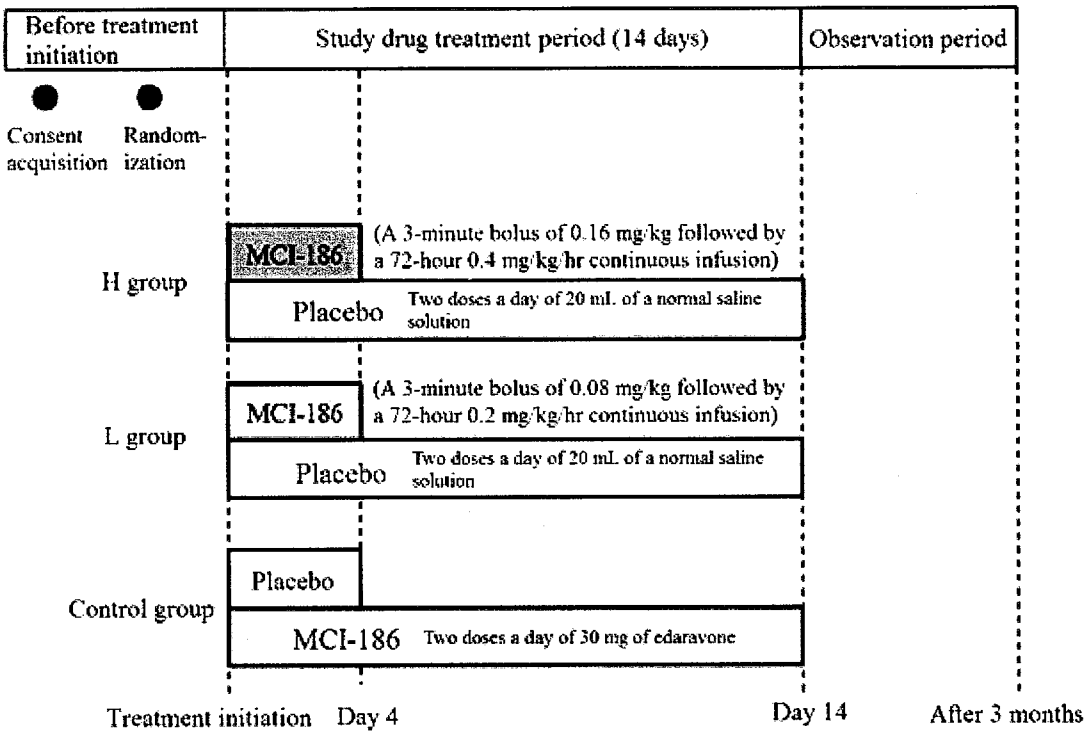
(19) Patients weighing ≥ 100 kg (rounded to the nearest whole number)

(20) Other patients judged by the investigator (or subinvestigator) to be ineligible as subjects of this study

4 Study Design

Study Phase : Phase II

Type of clinical trial : Confirmatory studies



5 Investigational product, Dose and Regimen

5.1 Investigational product Name

Study product

Name : MCI-186 Injection

Nonproprietary name : Edaravone (JAN)

Dosage forms and strengths: 1 ampule (20 mL) containing 30 mg of edaravone Colorless Clear, aqueous solution for injection

Name : MCI-186 Injection Placebo

Dosage forms and strengths: Clear and colorless aqueous injection indistinguishable from MCI-186 Injection, each ampoule containing 20 mL of physiological saline.

5.2 Dose and Regimen

Investigational product will be administered using a double-dummy technique with the following 2 dosing regimens:.

(1) Continuous IV Dosing

Six blinded ampoules (20 mL/vial) of investigational product are to be filled and prepared undiluted in an empty sterile bag (120 mL/bag), the infusion rate is to be determined based on the subject's body weight (rounded to the nearest whole number), and the infusion rate is to be administered as a 3-minute bolus infusion using an infusion pump, followed by 72 hours continuous IV infusion. The continuous infusion of the next bag should be started

immediately upon changing the continuous infusion bag.

(2) Approved dosage and administration

1 (20 mL) ampoule of blinded investigational product will be diluted with an appropriate volume of normal saline and administered as an IV infusion over 30 minutes twice daily in the morning and evening for 14 days. The approved dosing regimen should be started immediately after the start of the continuous IV dosing regimen. In principle, this drug should be administered for 14 days. However, after administration for 7 days after the start of administration and completion of NIHSS evaluation, administration of investigational product may be completed only when neurological symptoms due to the primary disease have resolved to the pre-onset state and stabilized, and when continuation of administration of investigational product is not clinically significant and the investigator (subinvestigator) judges that administration of Midi-chlorian can only result in disadvantages such as restraint of the subject.

The combinations of investigational product to be used in each group are as follows.

High dose continuous IV infusion group (H group): MCI-186 is administered as a bolus of 0.16 mg/kg over 3 minutes, followed by a continuous IV infusion at 0.4 mg/kg/hr for 72 hours. Placebo will be administered twice daily by IV infusion over 30 minutes.

Low dose continuous IV infusion group (L group): MCI-186 is administered as a bolus of 0.08 mg/kg over 3 minutes followed by a continuous IV infusion at 0.2 mg/kg/hr for 72 hours. Placebo will be administered twice daily by IV infusion over 30 minutes.

Approved dosage and administration group (control group): Placebo is administered by bolus injection over 3 minutes, followed by continuous intravenous infusion for 72 hours. In addition, MCI-186 30 mg is administered twice daily by IV infusion over 30 minutes.

5.3 Duration of Treatment

14 days

(Dosage and administration of continuous intravenous infusion: 72 hours, approved dosage and administration: 14 days)

6 Concomitant medications and therapies

Concomitant use of the following drugs and therapies is prohibited from the onset to the evaluation day 3 months after the onset.

6.1 Prohibited Medications

(1) Thrombolytics (rt-PA preparations, urokinase, etc.)

(2) Addition of edaravone formulation

(3) Any investigational product other than investigational product

6.2 Prohibited Concomitant Medications and Procedures

(1) Surgical treatment for cerebral infarction (Bypass surgery, carotid endarterectomy)

(2) Endovascular Treatment (Transarterial thrombolysis, angioplasty/thrombolysis using PTA balloon, intracranial stent placement, thrombus retrieval therapy, carotid artery stent placement)

(3) Continuous transcranial Doppler (TCD), hypothermia, hyperbaric oxygen, and experimental therapies with unestablished efficacy

7 Endpoints

7.1 Efficacy Endpoints

Primary Endpoint

NIHSS (for 7 days after onset)

Secondary Endpoints

(1) NIHSS (Day4, Day7, Day10, Day14, Week 3, Discharge, Month 3)

(2) mRS (3 weeks later, at discharge, 3 months later)

(3) BI (Day14, Week 3, Discharge, Month 3)

(4) FIM (3 weeks later, at discharge, 3 months later)

(5) Time to start rehabilitation

(6) Duration of hospitalization

(7) Brain imaging

Exploratory Endpoints

[redacted]

7.2 Safety Endpoints

(1) Adverse Events and Adverse Drug Reactions

(2) Neurological Examination

(3) General laboratory tests

(4) Vital signs

(5) Standard 12 lead ECG

8 Target sample size

A total of 336 subjects were randomized.

- H group: 120 subjects
- L group: 96 subjects
- Control group: 120 subjects

9 Study period

June 2017 to August 2019 (registration deadline: around February 2019)

10 Examination/Observation Schedule

Timing of evaluation	Before the start of treatment			Investigational product treatment period								Observation period		
	Consent	Eligibility Confirmation	Enrollment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 10	Day 14 OR Investigational product infusion At discontinuation [a]	Week 3 [b]	At discharge	3 months [c] OR Observation period At discontinuation
Acceptable range									±1 day	±1 day	+1 day	±2 days	-1 day	±8 days (+8 days)
Informed consent	●													
Demographics		●												
Enrollment/Allocation			●											
Investigational product infusion				←72 hours continuous IV infusion→										
				←Twice daily for 14 days [d]→										
NIHSS		●		←Assessed daily for 7 days after the start of treatment→						●	●	●	●	●
mRSe		●[f]										●	●	●
BI											●	●	●	●
FIM												●	●	●
[redacted]											●	●	●	●
Imaging		DWI T2*WI FLAIR MRA					DWI[g] T2*WI[g]				DWI T2*WI			FLAIR
Neurological Examination		●[h]									●	●	●	●
Standard 12 lead ECG		●				●[i]								
Vital signs		●				●[i]			●		●			
Laboratory tests (central measurement)		●				●[i]			●	●	●	●	●	
Laboratory tests (local laboratory)		●[j]		←Measured daily for 5 days after the start of administration [k]→										
PGx blood collection				●(Blood sampling will be performed once during the study period in subjects who consent to blood sampling for gene analysis.)										
Adverse Events				←→										
Concomitant medications		←→												

a) If the study is discontinued during the investigational product treatment period, the examination at discontinuation of the investigational product treatment period will be performed, and the safety of the subject will be evaluated 3 months after the onset wherever possible.

b) Week 3 is defined as Day 22 in this study. If the patient is discharged from the hospital within 3 weeks after the start of administration, the tests specified at the time of discharge will be performed, and the tests after 3 weeks will not be required.

c) For this study, 3 months after onset is defined as Day85. If the study is discontinued during the observation period, the examination at discontinuation of the observation period will be performed, and the safety of the subject will be evaluated 3 months after the onset wherever possible.

d) Administer twice daily in the morning and evening for 14 days. In principle, this drug should be administered for 14 days. However, after administration for 7 days after the start of administration and completion of NIHSS evaluation, administration of investigational product may be completed only when neurological symptoms due to the primary disease have resolved to the pre-onset state and stabilized, and when continuation of administration of investigational product is not clinically significant and the investigator (subinvestigator) judges that administration of the drug can only result in disadvantages such as restraint of the subject (discharge from the hospital is not allowed).

e) Evaluation of mRS was performed using Cerebrovasc Dis 2006.; The Japanese version of the mRS questionnaire published in 21:271-278 (Attachment 2 "mRS Interview Form ", Attachment 3" mRS Assessment Criteria Form ") will be used.

f) Collect pre-onset mRS.

g) To be photographed after the end of 72 hours continuous intravenous infusion (+2 days).

h) A neurological examination will be performed once between informed consent and Day 5.

i) Standard 12 lead ECGs, vital signs, and laboratory assessments (central laboratory) will be obtained before the end of the 72 hours infusion (Day -1).

j) Only white blood cell count (WBC), red blood cell count (RBC), hematocrit (Ht), hemoglobin (Hb), platelets (Plt), AST (GOT), ALT (GPT), LDH, ALP, γ-GTP, total bilirubin (T-Bil), CK (CPK), urea nitrogen (BUN), serum creatinine (Cre), and eGFR will be examined urgently in the hospital to confirm the eligibility as a case.

k) Only red blood cell (RBC), platelet (Plt), AST (GOT), ALT (GPT), LDH, ALP, total bilirubin (T-Bil), CK (CPK), urea nitrogen (BUN), and serum creatinine (Cre) will be measured in the hospital every day for 5 days from the start day of treatment to confirm the safety of subjects.

1. History of the Protocol and Background Information

(1) Target disease and its treatment method

According to [1] Summary of the Patient Survey in 2014 and [2] Summary of Vital Statistics 2014 by the Ministry of Health, Labour and Welfare, the number of patients with cerebrovascular disease and the number of deaths from cerebrovascular disease in Japan are 1179000 and 114000, respectively, being the 4th leading cause of death in Japan, and the number of deaths from cerebral infarction has been reported to be 66000. In addition, it has been reported that cerebrovascular disease was the number one cause of the need for support and nursing care and accounted for approximately 19% of them in [3] of the General Conditions of National Living Survey 2013, and that cerebrovascular disease was the cause in approximately 22% of the people requiring nursing care, and that the amount of medical expenses for medical care for cerebrovascular disease was 1.7 trillion yen in [4] of the General Conditions of National Medical Expenses in 2013. Among acute ischaemic stroke patients excluding TIA, about 75% of all patients are reported to be cerebral infarction patients [5].

Patients in the acute ischaemic stroke have disturbance of consciousness and movement, and at first, general respiratory, circulatory, and metabolic management is performed in emergency wards or stroke wards, and at the same time, medical treatment for cerebral infarction is mainly performed. They have been treated with thrombolytics, neuroprotectants (edaravone), anticerebral edema agents, anticoagulants (Argatroban, heparin, etc.), and antiplatelet agents (Aspirin, Ozagrel Sodium, etc.). The use of thrombolytic agents (rt-PA) is limited and contraindicated by the treatable time after onset (within 4.5 hours) and the risk of haemorrhagic adverse events. The proportion of patients using these agents is estimated to be about 5% of all patients. In addition, endovascular treatment (There are conditions such as prioritizing treatment with rt-PA and performing it for patients within 8 hours after onset among patients who are non-responsive or off-label, and conditions of study sites and study doctors.) is being performed for patients in the acute ischaemic stroke, but the number of patients treated is limited due to the conditions of use and indications.

In recent years, advances in diagnostic techniques such as magnetic resonance imaging (MRI) have improved the understanding of acute ischemic stroke conditions, such as pathological changes over time in infarct foci. At present, it is said that the infarct foci are completed in about 1 day after the attack [6], that the hypoperfusion site around the infarct foci (penumbra) is present for about 2 days and leads to infarction after that [7, 8], and that the plasma concentration of oxidized LDL, an oxidation marker, is high for 3 days after the onset [9]. In the case of radical scavengers such as this drug, the effect of treatment may be more effective to maintain sufficient blood concentrations at an early stage after onset to prevent oxidative damage in the hyperacute phase until infarction enlarges and completes. If neurological symptoms are improved early, early mobilization and early start of rehabilitation may be possible, which may lead to prevention of disuse syndrome, early improvement of ADL and social rehabilitation. It is also expected that patients and their families will benefit greatly if the length of hospital stay at acute care hospitals is shortened and the amount of discharge assistance is reduced.

(2) Investigational product Name and Description

Edaravone has good radical scavenging activity against hydroxyl and peroxyl radicals, etc. in *in vitro*, and also has lipid peroxidation inhibitory action and cell damage protective action based on radical scavenging activity. In addition, MT-MD001 showed a cerebral protective effect against nerve cell death, cerebral infarction, cerebral edema, neurological symptoms, etc. in *in vivo*, and these effects are considered to be due to the reduction of oxidative stress in the body by radical scavenging activity.

(3) Nonclinical and Clinical Studies

1) Nonclinical Studies (Pharmacology)

[redacted]

2) Nonclinical Studies (Toxicology)

[redacted]

[redacted]Clinical study [redacted]

[redacted]Clinical study [redacted]

[redacted]

(4) Investigational Plan

Based on the results of Study MCI-186-E04, this study designed a multicenter, randomized, double-blind, approved dose-regimen controlled, parallel-group study in Japanese patients with acute ischaemic stroke to evaluate the efficacy and safety of the dosage regimen of 3-minute bolus administration followed by continuous intravenous infusion.

2. Study Objectives

To evaluate the efficacy and safety of MCI-186 administered by bolus injection followed by 72 hours continuous intravenous infusion in patients with acute ischaemic stroke in a double-blind, parallel-group, comparative study of the approved dosage and administration of MCI-186 as a control.

3. Subjects

3.1 Subjects

Patients with acute ischaemic stroke within 24 hours after onset

3.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria at the time of enrollment:.

(1) Patients who have provided appropriate written consent to participate in the study by themselves or their legally acceptable representatives

(2) Patients aged 20 to 85 years, inclusive, at the time of informed consent

(3) Patients who can start receiving investigational product within 24 hours after onset

(4) Patients with new ischemic areas confirmed by MRI only in the tentorium

(5) Patients with neurological symptoms defined as NIHSS ≥ 4 and ≤ 22

[Rationale]

(1) This criterion was specified to comply with "Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs, " Ministerial Ordinance No. 28 by the Ministry of Health and Welfare, dated March 27, 1997.

(2) This criterion was set based on the facts that cerebral infarction rarely occurs in minors and that subjects aged 20 years or older can decide whether or not to participate in the study on their own will when obtaining consent. Also, since many fatal cases have been reported in the elderly, the upper age limit was set at 85 years in order to select patients for whom the safety and efficacy can be appropriately evaluated.

(3) The dosage and administration were selected in accordance with the indication and dosage and administration specified in the package insert of edaravone.

(4) (5) To select patients in whom the efficacy of this drug can be appropriately evaluated.

3.3 Exclusion Criteria

Patients who meet any of the following exclusion criteria at enrollment will be excluded from the study.

(1) Patients with a pre-existing disorder equivalent to mRS ≥ 2

(2) Patients being treated with antibiotics for infections at the time of enrollment

(3) Patients who have received or are scheduled to receive treatment with prohibited concomitant drugs (thrombolytics, etc.) or prohibited concomitant therapies (Endovascular treatment, surgical treatment, etc.) for primary disease

(4) Patients for whom the investigator (subinvestigator) judges that the efficacy endpoints (NIHSS, mRS, BI, etc.) set in this study cannot be appropriately evaluated. For example, patients in whom improvement of NIHSS ≥ 4

points cannot be expected due to neurological symptoms existing from before the onset of acute ischaemic stroke, patients with Alzheimer's type dementia, patients with Parkinson's disease, etc.

(5) Patients with severe disturbance of consciousness (Japan Coma Scale ≥ 100)

(6) Patients who are clearly complicated with peripheral vascular disease or peripheral neuropathy and cannot undergo neurological examination in the investigator's (subinvestigator's) opinion

(7) Patients with severe renal disorder (e.g., eGFR < 30)

(8) Patients with severe hepatic disorder (Patients with ALT, AST, or γ-GTP exceeding 2.5 times the upper limit of normal, etc.)

(9) Platelet count < 100,000/mm ^{3}

(10) Patients diagnosed with a disease other than acute ischaemic stroke (Intracranial hemorrhage, subarachnoid hemorrhage, arteriovenous malformation, moyamoya disease, brain tumor, etc.) or cerebral aneurysm with a maximum diameter of > 7 mm by MRI on admission

(11) Patients with a history or complication of drug abuse or alcohol dependence

(12) Patients with a history or complication of malignant tumor within 5 years after the onset of acute ischaemic stroke

(13) Patients with a history of hypersensitivity to edaravone formulations

(14) Patients with a cardiac disease requiring inpatient treatment (e.g., acute myocardial infarction, cardiac failure), who have a problem in general condition, and who are judged by the investigator (subinvestigator) to be ineligible for treatment with this study

(15) Patients in whom MRI scan cannot be performed

(16) Male patients and female patients of childbearing potential who do not agree to use birth control from the day of informed consent to the day after the last dose of investigational product

(17) Patients who are pregnant, breastfeeding, or possibly pregnant

(18) Patients who have received any other investigational product within 12 weeks before informed consent

(19) Patients weighing ≥ 100 kg (rounded to the nearest whole number)

(20) Other patients judged by the investigator (or subinvestigator) to be ineligible as subjects of this study

[Rationale]

(1) This criterion was set because patients with mRS ≥ 2 from before the onset are unlikely to have a good functional prognosis.

(2) This criterion was set in consideration of the safety of subjects because patients with infections may experience acute renal failure or aggravation of renal impairment due to deterioration of general condition, and concomitant use of antibiotics may exacerbate renal impairment.

(3) This criterion was set to exclude factors that may affect the evaluation of drug efficacy.

(4) This criterion was set to exclude patients for whom efficacy could not be appropriately evaluated.

(5) Since many fatal cases have been reported in patients with severe consciousness disorder and the incidence of renal disorder or liver disorder is high, these criteria were set in consideration of the safety of subjects.

(6) This criterion was set because appropriate neurological examination could not be performed.

(7) (8) (9) These criteria were set in consideration of the safety of subjects based on the package insert of RADICUT.

(10) These criteria were set to exclude diseases other than acute ischaemic stroke and to assure the safety of subjects because unruptured acute ischaemic stroke exceeding 7 mm in maximum diameter have a high risk of rupture [11, 12].

(11) This criterion was specified because efficacy and safety could not be appropriately evaluated.

(12) This criterion was set because patients are inappropriate as subjects because they are prone to aggravation of general condition and complications/accompanying symptoms, which may make it difficult to evaluate prognostic effects.

(13) (14) These criteria were set in consideration of the safety of subjects based on the package insert of RADICUT.

(15) This criterion was specified because MRI imaging is essential in this study, and the eligibility of patients who cannot undergo MRI cannot be determined.

(16) (17) This criterion was set because the safety of this drug in pregnant women, fetuses, and infants has not been established.

(18) This criterion was specified because the effect of investigational product, for which evaluation has not been established, on the evaluation of the efficacy and safety of this drug is unpredictable.

(19) This was adopted because the design of investigational product in this study does not allow administration of the specified dose to subjects weighing 100 kg or more.

(20) These criteria were set to ensure the safe and ethical conduct of the study.

4. Subject Information and Consent

4.1 Preparation of Written Information and Informed Consent Form

The investigator prepares the written information for subjects and the informed consent form (hereinafter referred to as the informed consent form). The informed consent form will be an integrated document or a set of documents, which will be revised if necessary.

The prepared and revised documents should be submitted to the sponsor and approved by the IRB before the start of the study.

4.2 Contents to be included in the written information

The written information shall include at least the following items:

(1) That the study involves research

(2) Study objectives

(3) Name, title, and contact information of the investigator or subinvestigator

(4) How dose this study work? (Includes the experimental aspects of the study, subject selection criteria, and the probability of assignment to each treatment, if randomized.)

(5) The expected clinical benefits and foreseeable risks or inconveniences (When there is no intended clinical benefit to the subject, the subject should be made aware of this.)

(6) Availavlability of other treatment options for the patient and their possible important benefits and risks

(7) The expected duration of the subject's participation in the study

(8) That the subject's participation in the study is voluntary and that the subject or the subject's legally acceptable representative may refuse to participate in or withdraw from the study at any time. That the subject will not be disadvantaged by refusal or withdrawal or will not lose benefits to which the subject is otherwise entitled.

(9) That the monitors, auditors, IRB, etc. and domestic and overseas regulatory authorities will have access to source documents related to medical care. At that time, the confidentiality of subjects will be protected. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(10) That the subject's identity will remain confidential if the results of the study are published.

(11) The person to contact at the study site for further information regarding the study and the rights of subjects or in the event of study-related injury

(12) The compensation and treatment available to the subject in the event of study-related injury

(13) Type of IRB that investigates and reviews the appropriateness, etc. of the study, matters to be investigated and reviewed by each IRB, and other matters related to the IRB involved in the study

(14) Planned number of subjects participating in the study

(15) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's or the subject's legally acceptable representative's willingness to continue participation in the study

(16) The circumstances or reasons under which the subject's participation in the study may be terminated

(17) The anticipated expenses, if any, to the subject for participating in the study

(18) The anticipated prorated payment, if any, to the subject for participating in the study (including how to calculate the payment)

(19) The subject's responsibilities

4.3 Method of Obtaining Informed Consent

(1) Prior to the conduct of the study, the investigator (subinvestigator) will hand the informed consent form approved by the IRB to the patient himself/herself and provide sufficient explanation. The study collaborator can also provide supplementary explanation. The explanation must be given based on the written information for this study using language as plain as possible so that the patient can understand it, and the patient's questions must be fully answered. After confirming that the patient has fully understood the contents, the patient's written voluntary consent to participate in the study will be obtained. If the patient himself/herself is unable to give consent due to disturbance of consciousness or other reasons, the same explanation as above shall be given to a person who can give consent on behalf of the patient (legally acceptable representative *), and written consent shall be obtained. In such a case, the Investigator (or Subinvestigator) will obtain written informed consent after carefully considering whether the prospective legally acceptable representative is a person in the best interest of the subject, such as a person with parental authority, a spouse, a guardian, or their equivalent. In addition, if consent is obtained from the subject's legally acceptable representative, the subject's willingness to continue participation in the study will be confirmed in writing according to the improvement of the subject's understanding.

(2) The informed consent form will be signed (or signed and sealed) and dated by the investigator (or subinvestigator) who has provided the explanation and the patient or the patient's legally acceptable representative. If a study collaborator has provided supplementary explanation, the study collaborator will also sign (or sign and seal) and date the informed consent form.

(3) If the patient or his/her legally acceptable representative is unable to read the written information, the investigator (subinvestigator) will give sufficient explanation in the presence of an impartial witness and obtain his/her voluntary consent. The witness must also sign and date the informed consent form.

(4) Prior to the subject's participation in the study, the investigator (subinvestigator) will provide the subject or the subject's legally acceptable representative with a signed and dated informed consent form and appropriately retain the original informed consent form in accordance with the rules at the study site concerned.

(5) The date of informed consent will be recorded in the CRF.

*A legally acceptable representative is a person in whom the best interests of the subject are concerned in terms of real life and emotional collaboration between the subject and the subject's legally acceptable representative, such as a person with parental authority, a spouse, a guardian, or their equivalents. Therefore, persons directly or indirectly involved with this study (Physicians, nurses, etc.) cannot be legally authorized representatives.

4.4 Revision of Informed Consent Form

(1) If new important information becomes available that may be relevant to the subject's consent, the investigator (subinvestigator) will promptly provide this information orally to the subject already participating in the study or his/her legally acceptable representative, confirm whether or not to continue participation in the study, and record it in the medical record.

(2) The investigator will promptly determine the necessity of revision of the informed consent form based on the information.

(3) If the investigator considers it necessary to revise the informed consent form, the investigator must promptly revise the informed consent form and obtain approval from the IRB again.

(4) The investigator (subinvestigator) will explain the study to subjects already participating in the study or their legally acceptable representatives using the informed consent form approved by the IRB again and obtain written voluntary consent to continue participation in the study from the subjects or their legally acceptable representatives.

(5) As with the initial informed consent, the investigator (or subinvestigator) who provided the explanation, the subject, or the subject's legally acceptable representative will sign (or sign and seal) and personally date the informed consent. If a study collaborator has provided supplementary explanation, the study collaborator will also sign (or sign and seal) and date the informed consent form.

(6) As with the initial informed consent, if the subject or the subject's legally acceptable representative is unable to read the written information, the investigator (subinvestigator) will provide sufficient explanation in the presence of an impartial witness and obtain the consent of the subject based on his/her free will. The witness must also sign and date the informed consent form.

(7) The Investigator (or Subinvestigator) will provide the subject with the sealed or signed and dated informed consent form and appropriately retain the original informed consent form in accordance with the rules at the study site concerned.

5. Study Design

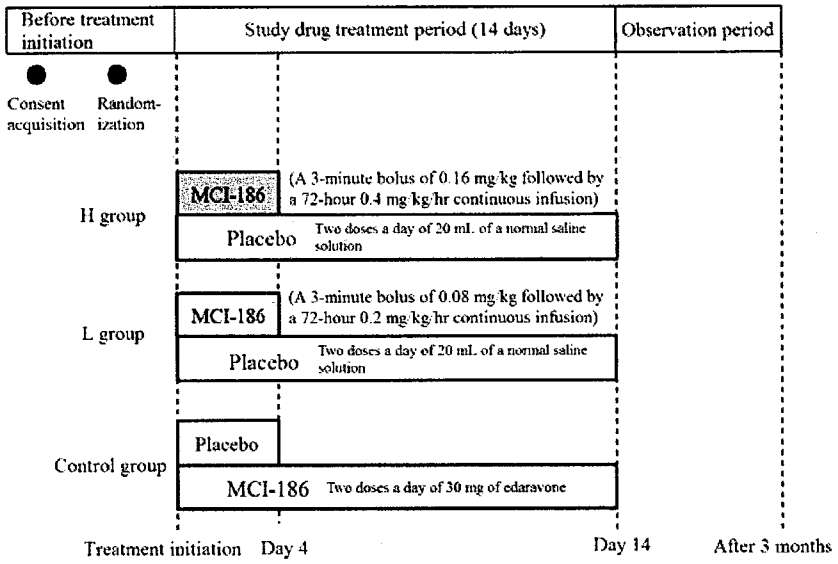
5.1 Study Phase and Type

Study Phase Phase II

Type of clinical trial : Confirmatory studies

5.2 Study Design

Multicenter, randomized, double-blind, parallel-group study using the approved dosage and administration



In this study, the eligibility of subjects will be confirmed promptly after informed consent, and subjects who meet the inclusion criteria will be randomly assigned to either the continuous intravenous infusion high-dose group (Group H), the continuous intravenous infusion low-dose group (Group L), or the approved dosage and administration group (Control group). Details of the dose and regimen of investigational product for each group are described in "8.3 Dose and regimen."

All subjects will be hospitalized from the date of informed consent and will remain hospitalized until Day14. If the administration of investigational product has been completed and the tests and assessments specified for Day14 and discharge have been completed, the subject can be discharged from the hospital if it is judged that the subject is ready for discharge based on the clinical judgment of the investigator (subinvestigator), and the subject will return to the hospital to undergo tests and examinations 3 months after the onset.

[Rationale]

In order to objectively evaluate the efficacy and safety of the 72 hours continuous intravenous infusion dosage regimen,

this study was designed as a parallel-group comparison study using the approved dosage regimen as a control. In order to minimize bias in the evaluation, it was decided to administer investigational product using a double-dummy method and conduct the study in a randomized double-blind manner.

5.3 Methods including blinding and randomization

5.3.1 Blinding

(1) Control of material list and randomization key code table

The contract randomization organization will prepare a material list (corresponding list of drug numbers and investigational product types) and a randomization key code table (corresponding list of allocation order numbers and treatment groups). In addition, a copy of the material list shall be provided to the CMC department of the sponsor for assignment to investigational product (assignment of drug numbers to investigational product).

The contract randomization organization will keep the material list and the randomization key code table under lock and key until key code breaking. The CMC department of the sponsor shall keep a copy of the material list under lock and key until key code breaking.

(2) Confirmation of indistinguishability of investigational product

CMC department of the sponsor shall assign drug numbers to investigational product (investigational product assignment) based on the contents of the material list in accordance with the sponsor's GMP standard operating procedure. The appearance of study product and the packaging form of investigational product will be checked for indistinguishability.

(3) Management of emergency key and SUSAR key

The emergency key will be opened at the discretion of the investigator and the personnel engaged in study safety management at the sponsor in the case where it is necessary to identify the treatment group urgently due to occurrence of a serious adverse event or safety concern that may affect the risk/benefit of investigational product concerned and identification of the investigational product is urgently needed (see "7.5 Emergency key opening procedure").

The key information at the time of SUSAR reporting to overseas regulatory authorities (SUSAR key) will be opened with the approval of the Unblind Responsible Person of the sponsor to determine the necessity of reporting to overseas regulatory authorities. In this case, the blind of the case will be maintained for all subjects, study sites, and the sponsor.

The emergency key and the SUSAR key will be prepared by the contract randomization organization and provided to the emergency contact center manager and the Mitsubishi Tanabe Safety Information Emergency Key Code Reception Center, respectively.

The emergency contact center manager and the Mitsubishi Tanabe Safety Information Emergency Code Reception Center manager will keep the emergency key and the SUSAR key under lock and key and control them

until key code breaking, respectively.

5.3.2 Method of Randomization and Allocation

Subjects whose eligibility based on the inclusion/exclusion criteria is confirmed will be randomly assigned to 3 treatment groups (Groups H, L, and control). At this time, subjects will be randomly assigned to either the H group, the L group, or the control group in a ratio of 5:4:5 by the stratified block method, using "NIHSS score at enrollment (NIHSS score of 4 to 9/10 to 15/16 -22)" which is considered to affect the evaluation of drug efficacy, as the stratification factor. Randomization will be based on the randomization key code table prepared by the contract randomization organization.

5.4 Endpoints

5.4.1 Efficacy Endpoints

Primary Endpoint

NIHSS (for 7 days after onset)

Secondary Endpoints

(1) NIHSS (Day4, Day7, Day10, Day14, Week 3, Discharge, Month 3)

(2) mRS (3 weeks later, at discharge, 3 months later)

(3) BI (Day14, Week 3, Discharge, Month 3)

(4) FIM (3 weeks later, at discharge, 3 months later)

(5) Time to start rehabilitation

(6) Duration of hospitalization

(7) Brain imaging

Exploratory Endpoints

[redacted]

[Rationale]

Primary Endpoint

The NIHSS was selected because it has been used widely in Japan and overseas in routine clinical practice and clinical studies for cerebral infarction as a scale to objectively evaluate neurological symptoms of cerebral infarction for each symptom, and its reliability and validity of evaluation have been recognized [13]. To investigate the efficacy in the early stage of onset, NIHSS will be measured daily until Day7 to compare the time course.

Secondary Endpoints

(1) Neurological symptoms will be compared at the following time points: Day4, Day7, Day10, Day14, Week 3, discharge, and Month 3.

(2) The mRS was selected because it is widely used in daily clinical practice and clinical studies of cerebral infarction in Japan and overseas as a rating scale for functional prognosis and its reliability and validity are recognized [14]. To investigate the effect of this drug on long-term functional prognosis of cerebral infarction, the evaluation time points were set at 3 weeks and 3 months.

(3) The BI [15] was selected because it is one of the representative basic activities of daily living (ADL) assessments and widely used in clinical studies of cerebral infarction [16].

(4) The FIM [17] is used in rehabilitation as a functional independence measure, and can evaluate the patient's condition (level of independence and amount of care) objectively and in more detail than other ADL scales.

(5) In order to prevent disuse syndrome and improve ADL and return to society at an early stage, stroke treatment guidelines strongly recommend aggressive rehabilitation as early as possible after the onset of stroke under sufficient risk management.

(6) Hospitalization was selected because it limits patients' life and social activities.

(7) To evaluate the differences in the efficacy of the 72 hours continuous intravenous infusion dosing regimen versus the approved dosing regimen for infarct lesion volume, cerebral edema, and intracranial hemorrhage.

Exploratory Endpoints

[redacted]

5.4.2 Safety Endpoints

(1) Adverse Events and Adverse Drug Reactions

(2) Neurological Examination

(3) General laboratory tests

(4) Vital signs

(5) Standard 12 lead ECG

[Rationale]

Because delayed neurotoxicity was observed in nonclinical studies of this drug, in addition to general safety endpoints, a neurological examination was included to check for the development of symptoms due to neuropathy of peripheral nerves and notochord.

6. Target Sample Size and Study Duration

6.1 Target sample size

A total of 336 subjects were randomized.

- H group: 120 subjects
- L group: 96 subjects
- Control group: 120 subjects

[Rationale]

[redacted]

In consideration of the above, it was decided to secure 96 subjects per group, including dropouts, as the number of subjects necessary for verification of superiority of early efficacy, and 120 subjects per group was set for the H group and the control group in order to increase the accuracy of searching for an improvement trend in long-term efficacy.

6.2 Study period

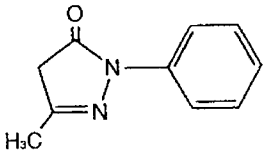
June 2017 to August 2019 (registration deadline: around February 2019)

7. Investigational product

7.1 Investigational product Name

Study product

Name	MCI-186 Injection
Nonproprietary name	Edaravone (JAN)
Dosage forms and strengths	1 ampule (20 mL) containing 30 mg of edaravone Colorless Clear, aqueous solution for injection



Name	MCI-186 Injection Placebo
Dosage forms and strengths	Clear and colorless aqueous injection indistinguishable from MCI-186 Injection, each ampoule containing 20 mL of physiological saline.

7.2 Packaging and Labeling of investigational product

(1) Packaging

1) Investigational product Packaging for Continuous IV Dosing

Six ampoules to be filled and prepared in 1 sterilized empty bag are packaged in a small box (Figure 7.2-1), and 8 small boxes and 8 sterilized empty bags are packed in a large box together with the small box packaged. For investigational product in Group H, all 6 ampoules are MCI-186; for investigational product in Group L, 3 ampoules are MCI-186 and 3 ampoules are placebo; and for investigational product in the control group, all 6 ampoules are placebo. Two large boxes of investigational product for continuous intravenous infusion per subject will be used. Figure 7.2-2 shows the arrangement of the large boxes. The upper part contains 8 small boxes of ampules, and the lower part contains small boxes of sterilized empty bags.

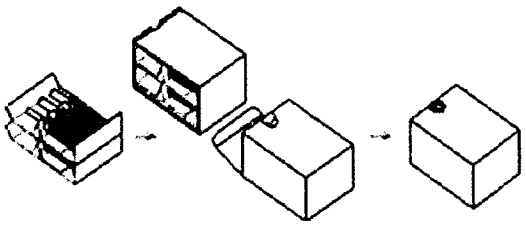


Figure 7.2. -1 Small Box Packaging (investigational product for Continuous IV Infusion)

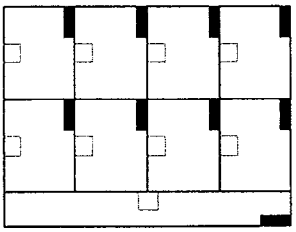


Figure 7.2-2 Packaging of a large box (investigational product for continuous intravenous infusion)

2) Investigational product package for approved dosage and administration

Package 2 ampoules of investigational product in a small box (Figure 7.2-3). In Groups H and L, both ampoules were placebo, and in the control group, both ampoules were MCI-186. One large box will be used for investigational product of the approved dosage and administration per subject. 16 small boxes are placed in a large box as shown in Figure 7.2-4.

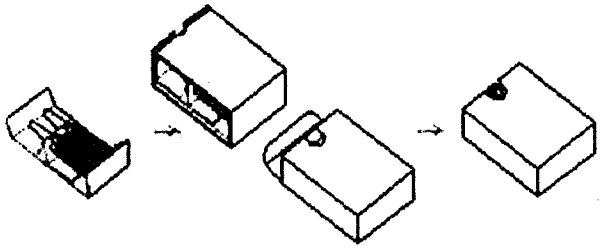


Figure 7.2-3 Small Box Packaging (investigational product for the approved dosage and administration)

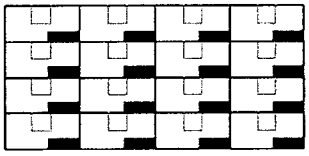


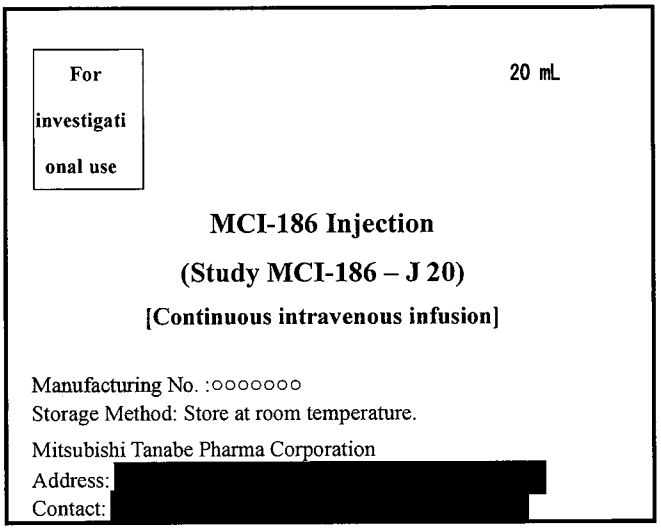
Figure 7.2-4 Packaging form of large box (investigational product with approved dosage and administration)

(2) Labeling

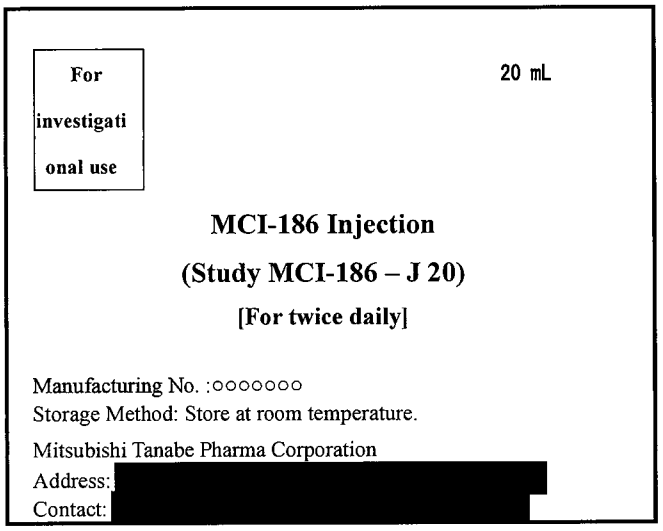
The following labels will appear on the ampoule and outside of the box. The small and large boxes will be labeled with the medication number.

1) Label for ampules

a) Continuous IV Dosing

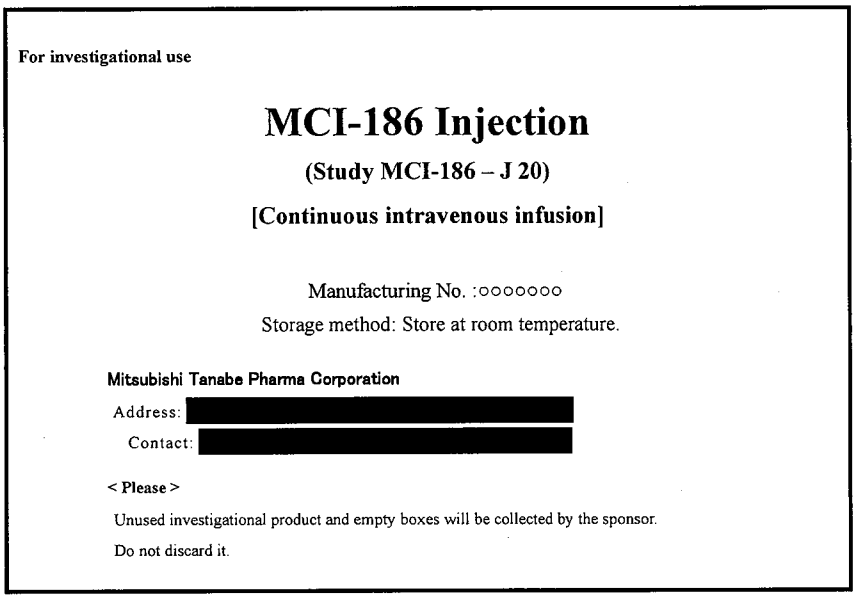


b) Approved dosage and administration

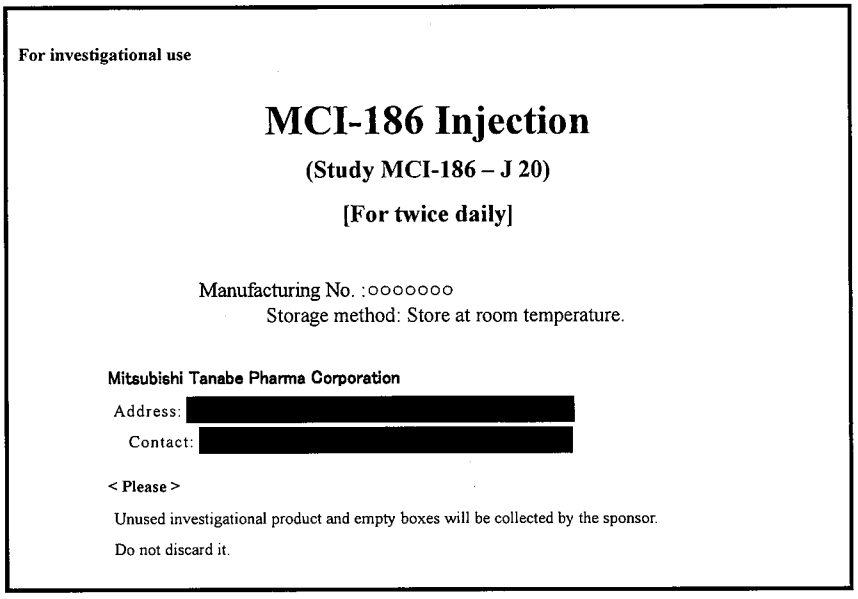


2) Small box label

a) Continuous IV Dosing



b) Approved dosage and administration



3) Large box label

a) Continuous IV Dosing

For investigational use

MCI-186 Injection

(Study MCI-186 – J 20)

[Continuous intravenous infusion]

Manufacturing No. :oooooooo

Storage Method: Store at room temperature.

< Please >

Unused investigational product and empty boxes
Until collected by the sponsor
Do not discard it.

Mitsubishi Tanabe Pharma Corporation
Address: [redacted]
Contact: [redacted]

b) Approved dosage and administration

For investigational use

MCI-186 Injection

(Study MCI-186 – J 20)

[For twice daily]

Manufacturing No. :oooooooo

Storage Method: Store at room temperature.

< Please >

Unused investigational product and empty boxes
Until collected by the sponsor
Do not discard it.

Mitsubishi Tanabe Pharma Corporation
Address: [redacted]
Contact: [redacted]

4) Packing box for empty bag

Continuous IV Dosing

For investigational use

Study MCI-186-J20

[For filling continuous intravenous infusion preparations]

8 empty bags

7.3 Storage method

Store at room temperature (1°C to 30°C)

7.4 Handling, Storage, and Control of investigational product

The sponsor will supply investigational product after the study contract is concluded with the study site. The investigational product manager will store and manage investigational product in accordance with the "investigational product Control Procedure" specified by the sponsor, and return unused investigational product to the monitor after the completion of the study.

Investigational product must not be used for any purpose other than those specified in this protocol (Other clinical studies, animal experiments, basic experiments, etc.).

7.5 Emergency key opening procedure

When identification of the relevant investigational product is necessary to ensure the safety of the subject because of occurrence of a serious adverse event or other reasons, the investigator shall respond in accordance with the "emergency key opening procedure." The investigator will promptly document the reason for unblinding in writing and submit it to the sponsor.

If any safety concern potentially affecting the risk-benefit of investigational product arises and identification of the relevant investigational product is urgently needed, the personnel engaged in study safety management at the sponsor shall respond in accordance with the "emergency key opening procedure". The personnel engaged in study safety management at the sponsor will record the reason for unblinding and contents of deliberation in accordance with the in-house procedures and retain the record.

8. Study methods for subjects

8.1 Preparation of subject screening, enrollment log, and identification code list

The investigator will prepare a subject screening list including all screened patients (patients who provided informed consent). Of these, subjects who provided informed consent will be given an identification code and a subject identification code list will be prepared. At that time, key information for collation with source documents shall be described.

The investigator will also prepare a subject enrollment list that includes sex, date of informed consent, and subject identification code of each subject enrolled in the study (Including subjects who discontinued or interrupted).

8.2 Subject Enrollment

The investigator (subinvestigator) will select patients who are considered eligible for this study and obtain written consent from subjects or their legally acceptable representatives in accordance with "4. Subject Information and Consent." The eligibility of subjects will be confirmed in accordance with the inclusion criteria and exclusion criteria. If the subject is judged to be eligible, the subject will be enrolled in the Web subject enrollment system. The registration center will confirm the information entered by the medical institution and return the randomization number of the drug to be administered to the investigator (subinvestigator) or the study collaborator. The registration center will also inform the sponsor and the contract monitoring organization of the randomization number. After confirming that the subject has been enrolled, the investigator (subinvestigator) will prescribe investigational product with the assignment number instructed by the registration center.

8.3 Dose and Regimen

Investigational product will be administered using a double-dummy technique with the following 2 dosing regimens:.

(1) Continuous IV Dosing

Six blinded ampoules (20 mL/bottle) of investigational product are filled and prepared without dilution in an empty sterile bag (120 mL/bag), the infusion rate is determined by the infusion rate calculated on the basis of the subject's body weight (rounded to the nearest decimal point) (Attachment 7: Infusion Rate Conversion Table), and the infusion rate is administered as a bolus injection using an infusion pump for 3-minute followed by a continuous intravenous infusion for 72 hours. The continuous infusion of the next bag should be started immediately upon changing the continuous infusion bag.

(2) Approved dosage and administration

1 (20 mL) ampoule of blinded investigational product will be diluted with an appropriate volume of normal saline and administered as an IV infusion over 30 minutes twice daily in the morning and evening for 14 days. The approved dosing regimen should be started immediately after the start of the continuous IV dosing regimen. In principle, this drug should be administered for 14 days. However, after administration for

7 days after the start of administration and completion of NIHSS evaluation, administration of investigational product may be completed only when neurological symptoms due to the primary disease have resolved to the pre-onset state and stabilized, and when continuation of administration of investigational product is not clinically significant and the investigator (subinvestigator) judges that administration of Midi-chlorian can only result in disadvantages such as restraint of the subject.

The combinations of investigational product to be used in each group are as follows.

High dose continuous IV infusion group (H group): MCI-186 is administered as a bolus of 0.16 mg/kg over 3 minutes, followed by a continuous IV infusion at 0.4 mg/kg/hr for 72 hours. Placebo will be administered twice daily by IV infusion over 30 minutes.

Low dose continuous IV infusion group (L group): MCI-186 is administered as a bolus of 0.08 mg/kg over 3 minutes followed by a continuous IV infusion at 0.2 mg/kg/hr for 72 hours. Placebo will be administered tgroupwice daily by IV infusion over 30 minutes.

Approved dosage and administration group (control group): Placebo is administered by bolus injection over 3 minutes, followed by continuous intravenous infusion for 72 hours. In addition, MCI-186 30 mg is administered twice daily by IV infusion over 30 minutes.

[Rationale]

The doses in Groups H and L in this study were selected with reference to [redacted]

8.4 Duration of Treatment

14 days

(Dosage and administration of continuous intravenous infusion: 72 hours, approved dosage and administration: 14 days)

In principle, this drug should be administered for 14 days. However, after administration for 7 days after the start of administration and completion of NIHSS evaluation, administration of investigational product may be completed only when neurological symptoms due to the primary disease have resolved to the pre-onset state and stabilized, and when continuation of administration of investigational product is not clinically significant and the investigator (subinvestigator) judges that administration of Midi-chlorian can only result in disadvantages such as restraint of the subject.

[Rationale]

Duration of administration of continuous intravenous infusion dosage and administration: It is said that the infarct foci are completed in about 1 day after cerebral infarction attack [6], it is also reported that the penumbra remains for about 2 days and leads to infarction later [7, 8], and that the plasma concentration of oxidized LDL, an oxidation marker, is high for 3 days after the onset [9]. The administration period was set at 3 days because it was considered that a sufficient blood concentration could be maintained at an early stage of 3 days after the onset until the infarct enlarged and completed, and higher efficacy could be obtained by scavenging radicals.

Duration of treatment with the approved dosage and administration: It was set to be 14 days based on the dosage and administration of RADICUT Injection 30 mg.

8.5 Concomitant medications and therapies

8.5.1 Prohibited Medications

Concomitant use of the following drugs is prohibited from the onset to the evaluation day 3 months after the onset.

(1) Thrombolytics (rt-PA preparations, urokinase, etc.)

(2) Addition of edaravone formulation

(3) Any investigational product other than investigational product

[Rationale]

(1) (2) This criterion was specified to possibly affect the efficacy evaluation.

(3) These criteria were set because they may affect the evaluation of efficacy and safety.

8.5.2 Prohibited Concomitant Medications and Procedures

Concomitant use of the following therapies is prohibited from the onset to the evaluation day 3 months after the onset.

(1) Surgical treatment for cerebral infarction (Bypass surgery, carotid endarterectomy)

(2) Endovascular Treatment (Transarterial thrombolysis, angioplasty/thrombolysis using PTA balloon, intracranial stent placement, thrombus retrieval therapy, carotid artery stent placement)

(3) Continuous transcranial Doppler (TCD), hypothermia, hyperbaric oxygen, and experimental therapies with unestablished efficacy

[Rationale]

This criterion was specified to possibly affect the efficacy evaluation.

8.5.3 Record concomitant medications and procedures

The investigator (subinvestigator) or a study collaborator will record the following contents of drugs and therapies used during the study period (from the onset to the evaluation day 3 months after onset) in the concomitant drugs and therapies section of the case report form. Saline, etc. for reconstitution of injections should not be recorded.

(1) Concomitant medications: Name of drug, route of administration, duration of administration, reason for use, daily dose (drug used for the primary disease)

(2) Concomitant therapies: name of therapy, duration of use, reason for use

8.6 Subject Management

(1) Lifestyle Guidance

The investigator (subinvestigator) or a study collaborator will give guidance to subjects with attention to the following points.

1) Subjects should be evaluated on the designated days. If the subject cannot visit the study site on the designated day, he/she must contact the investigator or study coordinator and follow his/her instructions.

2) Subjects should carry the study participation card with them and present it when they visit other hospitals or departments. Also, even if you are using drugs prescribed by your study doctor other than this study or drugs purchased at a pharmacy, you must tell the investigator (subinvestigator) or a collaborator. In addition, any new medication during the study must be reported to the investigator (subinvestigator) or study collaborator before use.

3) Subjects should notify the investigator or designee of any physical abnormalities.

4) The investigator (subinvestigator) or a study collaborator should instruct subjects to use reliable methods of contraception shown below from the day of informed consent to the next day after completion of administration of investigational product. Calendar, ovulation, symptothermal,

post-ovulation methods, and intravaginal methods are not acceptable methods of contraception. Postmenopausal women who have been amenorrheic for at least 1 year or women who have undergone surgical hysterectomy or bilateral oophorectomy are excluded.

1)Not having sex

2)Performing two effective methods of contraception. A barrier contraceptive (Oral contraceptives, intrauterine ring, tubal ligation, vasectomy, etc.) plus a more effective contraceptive method is recommended.

(2) Guidance related to evaluation 3 months after onset

When the subject is discharged from the hospital, the investigator (subinvestigator) or a study collaborator will instruct the subject (Family members, caregivers, site staff, etc. as needed) to return to the hospital 3 months after the onset to undergo specified evaluations and tests.

In addition, the investigator (subinvestigator) or a study collaborator will instruct subjects (Family members, caregivers, site staff, etc. as needed) to record the subject's condition immediately before the visit day 3 months after the onset in the patient diary, regarding the following information necessary for the evaluation of functional independence of subjects 3 months after the onset.

1) Self-care, degree of independence during excretion, transfer, and transfer

2) Independence level of communication and social awareness

9. Examination/Observation

9.1 Examination/Observation Schedule

The examination/observation schedule is shown in Table 9.1.1.

Table 9.1.1 Examination/Observation Schedule

Timing of evaluation	Before the start of treatment			Investigational product treatment period								Observation period		
	Consent	Eligibility Confirmation	Enrollment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 10	Day 14 OR Investigational product infusion At discontinuation [a]	Week 3 [b]	At discharge	3 months [c] OR Observation period At discontinuation
Acceptable range									±1 day	±1 day	+1 day	±2 days	-1 day	±8 days (+8 days)
Informed consent	●													
Demographics		●												
Enrollment/Allocation			●											
Investigational product infusion				←72 hours continuous IV infusion→										
				←Twice daily for 14 days [d]→										
NIHSS		●		←Assessed daily for 7 days after the start of treatment→						●	●	●	●	●
mRS[e]		●[f]										●	●	●
BI											●	●	●	●
FIM												●	●	●
[redacted]											●	●	●	●
Imaging		DWI T2*WI FLAIR MRA					DWIg T2*WIg				DWI T2*WI			FLAIR
Neurological Examination				●[h]							●	●	●	●
Standard 12 lead ECG		●					●[i]							
Vital signs		●					●[i]		●		●			
Laboratory tests (central measurement)		●					●[i]		●	●	●	●	●	
Laboratory tests (local laboratory)		●[j]		←Measured daily for 5 days after the start of administration [k]→										
PGx blood collection				●(Blood sampling will be performed once during the study period in subjects who consent to blood sampling for gene analysis.)										
Adverse Events				←→										
Concomitant medications		←→												

a) If the study is discontinued during the investigational product treatment period, the examination at discontinuation of the investigational product treatment period will be performed, and the safety of the subject will be evaluated 3 months after the onset wherever possible.

b) Week 3 is defined as Day 22 in this study. If the patient is discharged from the hospital within 3 weeks after the start of administration, the tests specified at the time of discharge will be performed, and the tests after 3 weeks will not be required.

c) For this study, 3 months after onset is defined as Day85. If the study is discontinued during the observation period, the examination at discontinuation of the observation period will be performed, and the safety of the subject will be evaluated 3 months after the onset wherever possible.

d) Administer twice daily in the morning and evening for 14 days. In principle, this drug should be administered for 14 days. However, after administration for 7 days after the start of administration and completion of NIHSS evaluation, administration of investigational product may be completed only when neurological symptoms due to the primary disease have resolved to the pre-onset state and stabilized, and when continuation of administration of investigational product is not clinically significant and the investigator (subinvestigator) judges that administration of the drug can only result in disadvantages such as restraint of the subject (discharge from the hospital is not allowed).

e) Evaluation of mRS was performed using Cerebrovasc Dis 2006.; The Japanese version of the mRS questionnaire published in 21:271-278 (Attachment 2 "mRS Interview Form ", Attachment 3 " mRS Assessment Criteria Form ") will be used.

f) Collect pre-onset mRS.

g) To be photographed after the end of 72 hours continuous intravenous infusion (+2 days).

h) A neurological examination will be performed once between informed consent and Day 5.

i) Standard 12 lead ECGs, vital signs, and laboratory assessments (central laboratory) will be obtained before the end of the 72 hours infusion (Day -1).

j) Only white blood cell count (WBC), red blood cell count (RBC), hematocrit (Ht), hemoglobin (Hb), platelets (Plt), AST (GOT), ALT (GPT), LDH, ALP, γ -GTP, total bilirubin (T-Bil), CK (CPK), urea nitrogen (BUN), serum creatinine (Cre), and eGFR will be examined urgently in the hospital to confirm the eligibility as a case.

k) Only red blood cell (RBC), platelet (Plt), AST (GOT), ALT (GPT), LDH, ALP, total bilirubin (T-Bil), CK (CPK), urea nitrogen (BUN), and serum creatinine (Cre) will be measured in the hospital every day for 5 days from the start day of treatment to confirm the safety of subjects.

9.2 Test/Observation Items and Timing

9.2.1 Items Related to Subject Demographics

The Investigator (or Subinvestigator) will investigate the following subject background factors before the start of treatment and record the details in the case report form. Even for items investigated after the onset but before obtaining informed consent, if the subject's consent to use the investigation results as pretreatment data in the study is obtained, the investigation results can be regarded as the investigation results at enrollment.

(1) Gender

(2) Date of birth (Western calendar)

(3) Weight

(4) Date and time of onset, date and time of visit, status at onset (Presence/absence of convulsion, clinical course, rationale for determination of cerebral infarction, etc.), disease type (Cardioembolic stroke, atherothrombotic cerebral infarction, lacunar infarction, other or indistinguishable)

(5) Level of consciousness disturbed: Japan Coma Scale(JCS, 3-3-9 degree system)

0: Clear

I: Awake (confusion, delirium, senselessness)

1. The patient was mostly alert, but it was not clear at all.

2. Disorientation (Time, place, person).

3. I cannot tell my name or date of birth.

II: Awakens to stimulus *(stupor, lethargy, hypersomnia, somnolence, drowsiness)

10. Open the eyes easily with an ordinary voice.

20. Open the eyes by loud voice or shaking.

30. Repeated calls with painful stimuli barely open the eyes.

*Consciousness after awakening will not be considered.

III: Does not awaken when stimulated (Deepcoma, coma, semicoma)

100. Discharge pain stimuli

200. Slight movement of hands and feet or grimacing due to painful stimuli.

300. Does not respond at all to painful stimuli.

(6) Medical history/complications

(7) Confirmation of eligibility

(8) Pre-symptomatic mRS(The subject or the subject's family will be interviewed.)

9.2.2 Administration status

The investigator (subinvestigator) or a study collaborator will confirm the administration status of investigational product and record the following items in the case report form.

(1) Continuous IV infusion rate, start and stop dates and times

(2) Date and time of starting administration of approved dosage and administration, and presence or absence of

completion of administration

(3) Stop date and time if treatment stopped

9.2.3 Items Related to Efficacy Evaluation

(1) NIHSS

NIHSS will be assessed before treatment, daily from Day1 (after the start of treatment) to Day7, on Day10, Day14, Week 3, at discharge, and 3 months later, and the date, time, and details of the assessment will be recorded in the case report form. The evaluator should be the investigator (subinvestigator) who has experience in evaluation in daily medical practice and has received a certain amount of training, and the same evaluator should evaluate each subject throughout the study period as much as possible.

(2) mRS

The Investigator (or Subinvestigator) will interview the subject according to the mRS Interview Form (Attachment 2) at 3 weeks, at discharge, and 3 months later, evaluate the mRS based on the assessment criteria form (Attachment 3), and record the date and contents of the evaluation in the case report form.

(3) BI

The investigator (subinvestigator) will assess BI on Day14, Week 3, at discharge, and 3 months later, and record the date and contents of the assessment in the case report form.

(4) FIM

FIM will be assessed 3 weeks later, at discharge, and 3 months later. The evaluator will be the investigator (subinvestigator) and study collaborator (occupational or physical therapist, etc.) who have received a certain amount of training, and the evaluation date and its contents will be recorded in the case report form.

(5) Period of starting rehabilitation

The Investigator (or Subinvestigator) must record in the CRF the date when the subject was released from bed and started rehabilitation.

(6) Duration of hospitalization

The investigator or subinvestigator will record the date of discharge, the place of discharge (Home, rehabilitation hospital, long-term care facility, etc.), and the reason for discharge in the case report form.

(7) Brain imaging

The investigator or the investigator's designee will obtain DWI, T2*WI, FLAIR, and MRA prior to dosing, DWI, T2*WI on Day4 (after completion of continuous IV infusion), DWI, T2*WI on Day14, and FLAIR 3

months later, and record the imaging dates in the CRF.

The infarct volume, degree of cerebral edema, and presence/absence and degree of intracranial hemorrhage will be evaluated by the Image Evaluation Committee.

[redacted]

9.2.4 Items Related to Safety Evaluation

9.2.4.1 Objective findings

(1) General laboratory tests: Hematology, serum chemistry, urinalysis

[Items to be measured from visit to before the start of administration]

The Investigator (or Subinvestigator) will perform emergency tests of the underlined items below in the hospital, confirm the eligibility as a subject, and record the date and time of blood sampling, date of confirmation of test results, and results of confirmation of test results (clinical significance) in the source documents. The date and time of blood sampling and test results will be recorded in the case report form.

In addition, all of the following tests will be measured at the contract laboratory testing institution, and the date of confirmation of the test results and the confirmation results (clinical significance) will be recorded. The test results provided by the contract laboratory testing institution will be retained by the study site and the sponsor.

The test items are as follows.

- Hematology: White blood cell count (WBC), Red blood cell count (RBC), Hematocrit (Ht), Hemoglobin (Hb), Platelets (Plt)
- Blood biochemistry: AST (GOT), ALT (GPT), LDH, ALP, γ-GTP, Total bilirubin (T-Bil), direct bilirubin (D-Bil), Total cholesterol (T-Cho), triglycerides (TG), total protein (TP), CK (CPK), Blood urea nitrogen (BUN), Serum creatinine (Cre), eGFR, Uric acid (UA), Na, K, Cl, albumin, glucose
- Urinalysis (qualitative): Sugar, protein, occult blood

[Items to be measured from the start of administration to the end of observation (3 months later)]

The Investigator (or Subinvestigator) must measure the underlined items below in the routine test in the hospital, confirm the test results, and record the date and time of blood sampling, date of confirmation of test results, and results of confirmation of test results (clinical significance) in the

source documents every day from Day1 (after the start of treatment) to Day5. The date and time of blood sampling and test results will be recorded in the case report form.

The investigator (subinvestigator) will measure all of the following tests at the contract laboratory testing institution on Day4 (before the end of continuous intravenous infusion), Day7, Day10, Day14, Week 3, and at discharge, and record the date of confirmation of test results and the results of confirmation (clinical significance). The test results provided by the contract laboratory testing institution will be retained by the study site and the sponsor.

The test items are as follows.

- Hematology: white blood cell count (WBC), red blood cell count (RBC), hematocrit (Ht), Hemoglobin (Hb), Platelets (Plt)
- Blood biochemistry: AST (GOT), ALT (GPT), LDH, ALP, γ-GTP, Total bilirubin (T-Bil), direct bilirubin (D-Bil), Total cholesterol (T-Cho), triglycerides (TG), total protein (TP), CK (CPK), Blood urea nitrogen (BUN), Serum creatinine (Cre), eGFR, Uric acid (UA), Na, K, Cl, albumin, glucose
- Urinalysis (qualitative): Sugar, protein, occult blood

(2) Standard 12 lead ECG

The investigator (subinvestigator) will perform standard 12 lead ECG at baseline and Day4 (before completion of continuous intravenous infusion) to determine whether there are any abnormal findings. The date and time of standard 12 lead ECG, ECG parameters (Heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc interval), and assessment results will be recorded in the CRF. Clinically significant abnormal findings, if determined by the investigator or subinvestigator, should be recorded as adverse events. The investigator will maintain ECG charts as source documents.

(3) Vital signs

The investigator/subinvestigator will measure systolic/diastolic blood pressure, pulse rate, and body temperature (Axillary, oral or tympanic body temperature) before administration, on Day4 (before the end of continuous intravenous infusion), Day7, and Day14, and record the date of measurement and the test results in the case report form. Blood pressure should be measured in the same arm throughout the study period whenever possible. Clinically significant abnormal findings, if determined by the investigator or subinvestigator, should be recorded as adverse events.

(4) Neurological Examination

The Investigator (or Subinvestigator) will perform a neurological examination on the healthy side once from the onset to Day5, and then on Day14, Week 3, at the time of discharge, and 3 months later. The tests that may be

affected by the subject's condition or treatment (Disturbance of consciousness, speech/articulation disorder, cognitive disorder, urinary catheter, etc.) will be performed on the day of observation, and the date and results will be recorded in the CRF.

NEUROLOGIC EXAMINATION (FUNCTIONAL)

- Sensory tests: Pain, sense of touch, sense of temperature, sense of vibration, sense of position
- Reflex function: Biceps brachii reflex, triceps brachii reflex, patellar tendon reflex, Achilles tendon reflex

Each item of the sensory test will be assessed according to the following criteria.

0: No abnormality

1: Weakening or disappearance in the fingers or toes

2: Weakness or disappearance up to the wrist or ankle

3: Decreased or disappeared up to the forearm or lower leg

4: Weakness or disappearance in the upper arm or thigh

Reflex function will be assessed according to the following criteria:.

0: No abnormality or increased

1: Decreased

2: Elimination

9.2.4.2 Adverse Events

Adverse events are clinically unfavorable or unintended signs (including clinically significant abnormal test values), symptoms, or diseases observed after administration of investigational product during the safety evaluation period, whether or not considered related to investigational product.

The investigator (subinvestigator) will investigate adverse events that occur in subjects from the start of administration of investigational product to the evaluation day 3 months after onset and record them in the case report form.

(1) Symptoms or Diseases

The investigator or subinvestigator will confirm the presence or absence of adverse events by interview and medical examination.

(2) Objective findings

Any clinically significant abnormality determined by the Investigator (or Subinvestigator) as * will be handled as an adverse event.

* "Clinically significant abnormalities " will be assessed according to the following criteria.

- If related to clinical signs or symptoms

However, if the symptom or sign has been separately reported as an adverse event, it is not necessary to regard the test abnormality as an adverse event.

- Medical or surgical intervention was performed for the abnormal test value.
- The administration method of investigational product is changed (Dose modification, suspension, discontinuation, etc.) due to the abnormal test value.
- Other clinically significant abnormalities as determined by the Investigator (or Subinvestigator)

(3) Adverse Event Assessment and Criteria

1) Start Date

The start date is defined as the date when the symptom is observed or the test date when the laboratory test abnormality is observed.

2) Severity

The severity of adverse events will be classified according to the following criteria:.

1. Mild: The event does not affect the subject's daily life.
2. Moderate: The event interferes with the subject's daily life to some extent.
3. Severe: The degree to which the event interferes with the subject's daily life.

3) Seriousness

The seriousness of adverse events will be classified as follows:.

1. Non-serious: Other than 2
2. Serious: a) to f) below
   a) Results in death
   b) Is life-threatening (The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe,.)
   c) Requires inpatient hospitalization or prolongation of existing hospitalization (Excluding admission for administrative or social reasons or for convenience of the subject)
   d) Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
   e) Is a congenital anomaly/birth defect
   f) is a medically important event or reaction (Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.).

4) Relationship to investigational product

The investigator will assess whether there is a "reasonable possibility" that investigational product may have caused the adverse event. The evaluation will be determined in consideration of causes other than investigational product such as the natural course of the underlying disease including the primary disease and complications, concomitant therapies, and other risk factors, as well as the temporal relationship between administration of investigational product and the onset of the event (Recurrence after readministration, disappearance after discontinuation, etc.). Adverse events for which a causal relationship with investigational product is assessed as "reasonable possibility" will be regarded as adverse drug reactions.

1. Reasonable possibility
2. No reasonable possibility

5) Outcome

The outcome of an adverse event is classified into the following 6 levels.

1. Recovered/Resolved
2. Recovering/Resolving
3. Not recovered/not resolved
4. Recovered/resolved with sequelae
5. Death
6. Unknown

6) Date of outcome

The date of outcome will be classified according to the following criteria.

Recovered/Resolved Date of recovery. However, if the date of recovery cannot be identified, it will be the date when the outcome is confirmed or determined.

Recovering/Resolving: Date on which remission was confirmed or determined

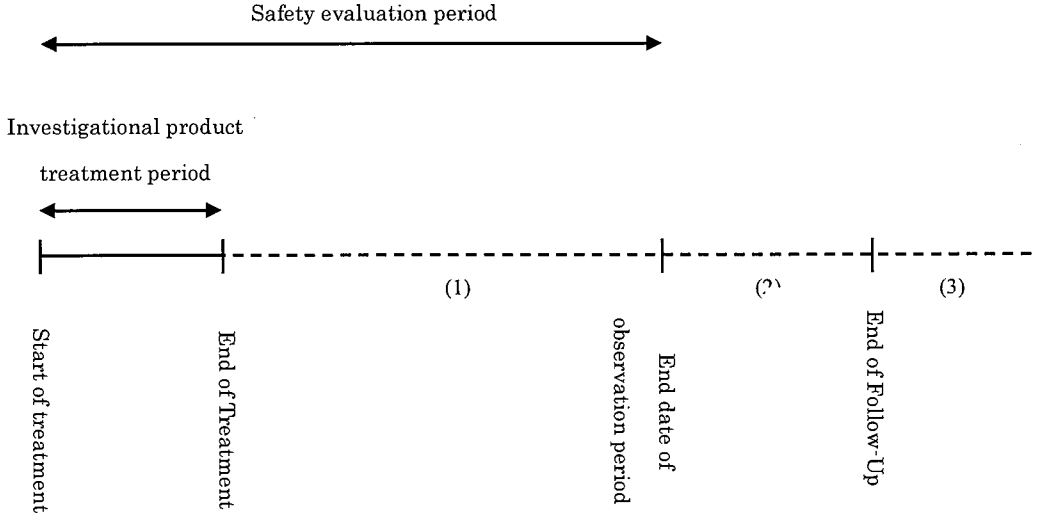
Not recovered/not resolved: Date of confirmation or determination of "not recovered"

Recovered/resolved with sequelae: Date when sequelae are confirmed or determined

Death Date of death. However, if the date of death cannot be identified, it will be the date when death is confirmed or determined.

Unknown Date of death if the outcome is unknown because the subject died from a cause other than the adverse event. For others, it is the date of confirmation or judgment.

7) Follow-up



- The safety evaluation period will be from the start date of treatment with investigational product to the end date of the observation period (the date when all specified 3-month evaluations are completed), and the presence or absence of adverse events will be investigated.

- The duration of the period (2) after the end of the observation period will be 14 days, and adverse events occurring during the safety evaluation period (treatment period with investigational product + (1)) will be followed up.
- The course of adverse events followed up during the period (2) after the end of the observation period should be recorded in the case report form.
- If an adverse event is resolving or not resolved, the date of outcome in the CRF should be the last day of observation during the period specified in (2).
- (2) For ADRs whose outcome is "recovering/resolving " or " not recovered/not resolved " at the end of the period specified in, the subsequent clinical course ((3)) will be investigated.
- If there is a valid reason for termination of the investigation after the end of the safety evaluation period (after the end of (1)), the reason will be recorded in the source documents, etc. and the follow-up investigation will be terminated.

(4) Items to be recorded in the case report form

If any adverse event is observed, the investigator (subinvestigator) will record the name of the adverse event *, date of onset, severity, seriousness, causal relationship with investigational product, details of treatment given (Drugs, therapies, etc.), outcome, and date of outcome in the adverse event section of the case report form. If the follow-up investigation is judged unnecessary because the outcome of an adverse event is "recovered/resolved " or" recovered/resolved with sequelae " or "death, " the reason should be recorded in the source document, etc. If the causal relationship with investigational product is "no reasonable possibility," the reason for the judgment will be recorded in the source document, etc.

* "Adverse event term " should be based on the following criteria:.
  - In principle, a diagnosis should be used.
  - If the diagnosis is unclear, the symptom should be used.
  - If multiple symptoms are present and can be described by a single diagnosis, the diagnosis should be used.
  - Surgical procedures, etc. are not regarded as adverse events. If a disease or symptom requiring surgical procedures, etc. is confirmed, it will be regarded as an adverse event.

9.2.5 Blood sampling for gene analysis

Blood sampling will be performed once at any time point from the start of investigational product to the evaluation day 3 months after the onset. The volume of blood to be collected will be approximately 8.5 mL (See "25.. Genetic analysis test" for details.).

10. Evaluation method and criteria

10.1 Efficacy

10.1.1 NIHSS

The NIHSS is a scale to objectively evaluate neurological symptoms of cerebral infarction and consists of 15 items: level of consciousness, disturbance of consciousness (Questioning, obedience), best gaze, visual field, facial paralysis, upper limb movements (right and left), lower limb movements (right and left), ataxia, sensation, best language, dysarthria, decreased extinction, and disturbance in attention. The total raw score of each item is 0~42 points, but if ataxia cannot be

performed, it is judged to be 0 points, and therefore the most severe case receives 40 points.

(See "5.4.1 Efficacy Endpoints," " 9.2.3 Efficacy Endpoints," and "Attachment 1 NIHSS.")

10.1.2 mRS

The mRS will evaluate the severity of sequelae after the onset of cerebral infarction on a 7-point scale from Grade 0 "No symptoms at all" to Grade 5 "Severe disorder" plus Grade 6 "Death."

(See "5.4.1 Efficacy Endpoints," " 9.2.3 Efficacy Endpoints," "Attachment 2: Questionnaire for mRS," and " Attachment 3: Assessment Criteria for mRS.")

10.1.3 BI

BI is a scale which evaluates 10 items of ADL (Feeding, transfer from wheelchair to bed, dressing, toileting, bathing, walking, going up and down stairs, dressing, bowel control, urinary control) with 5 points for each item, and the total score is 0~100 points.

(See "5.4.1 Efficacy Endpoints," " 9.2.3 Efficacy Endpoints," and "Attachment 4 BI.")

10.1.4 FIM

The FIM assesses 13 motor items and 5 cognitive items on a 7-point scale consisting of 1~7 items each. The motor items are divided into four major categories: self-care, excretion control, transfer, and movement. The total score is 18~126 points.

(See "5.4.1 Efficacy Endpoints," " 9.2.3 Efficacy Endpoints," and "Attachment 5 FIM.")

[redacted]

(See "5.4.1 Efficacy Endpoints," " 9.2.3 Efficacy Endpoints," and "[redacted]")

10.1.6 Brain imaging

Infarct lesion volume, degree of cerebral edema, and presence or absence of intracranial hemorrhage will be evaluated by the Image Evaluation Committee as follows.

Infarct volume will be measured on pre-dose DWI and 3-month FLAIR images.

Change in edema will be measured from the DWI findings on Day4 and Day14.

Presence/absence and severity of bleeding will be determined from T2*WI findings on Day4 and Day14.

The details will be specified in a separate written procedure.

10.2 Safety

10.2.1 Adverse events and adverse drug reactions (see "9.2.4.2 Adverse events" for details)

10.2.2 Neurological examination (see "9.2.4.1 Objective findings, (4) Neurological examination" for details)

11. Toxicity Management

11.1 Handling of serious adverse events

If any serious adverse event occurs during the period from the start of treatment with investigational product until the day of evaluation 3 months after the onset, the investigator (subinvestigator) will immediately provide appropriate treatment to the subject, regardless of the causal relationship with investigational product.

When an SAE occurs, the investigator or subinvestigator must immediately report it to the monitor (in writing in principle), and provide detailed information in writing to the sponsor within 7 days after the report. The investigator will also report the above SAE to the head of the study site.

The relationship between the definitions of serious adverse events shown in (PAB Notification No. 227 issued by the Director of the Evaluation and Licensing Division, ICH "Serious" criteria) and "Article 273 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" in "9.2.4.2 Adverse events" is as follows.

[Definition of serious adverse events]

"9.2.4.2 Adverse Events " PMSB/ELD Notification No. 227 issued by the Director of the Evaluation and Licensing Division, PMSB ICH Criteria for "Serious"		Quality and efficacy of drugs, medical devices, etc. and Act on Securing Safety Article 273 of the Enforcement Regulations
Results in death	↔	Death
Is life-threatening	↔	Is life-threatening
Requires inpatient hospitalization or prolongation of existing hospitalization	↔	Cases requiring admission to a hospital or clinic or prolongation of existing hospitalization for treatment
Results in persistent or significant disability/incapacity	↔	Disability
is a medically important event or reaction.	↔	Cases that may lead to disability
	↔	Serious cases in accordance with the above cases
Is a congenital anomaly/birth defect	↔	Congenital disease or anomaly in the next generation

11.2 Significant Adverse Events

For the purpose of examining the safety profile, AEs of special interest are defined as follows.

(1) Renal disorder

Serum creatinine >2.0 mg/dL

(2) Drug-induced liver injury

[19] if all of the following definitions of Hy's law are met:

a) AST or ALT > 3 × ULN

b) Total bilirubin > 2 times the upper limit of normal

c) ALP < 2 × ULN

d) There is no explanation for the above laboratory abnormalities a), b), and c) other than investigational product.

(3) Neurological disorders (medically significant changes on neurological examination in the healthy side)

If such an adverse event occurs, the investigator must inform the monitor immediately about the situation. The monitor will confirm with the investigator (subinvestigator) whether or not the study can be continued.

For significant adverse events, the sponsor will appropriately evaluate the occurrence status and frequency, and examine the appropriateness of study continuation and the necessity of protocol amendment.

11.3 Pregnancy reporting

If the investigator becomes aware that an embryo or fetus of a female subject may have been exposed to investigational product from the day of informed consent to the day after the completion of investigational product therapy, the investigator will immediately report it to the sponsor using the form designated by the sponsor (Attachment 8: Pregnancy Report). If the female subject wishes to give birth, the investigator will follow up until delivery as much as possible to investigate whether there is any effect of investigational product on the newborn, and report the details of the investigation to the sponsor using the pregnancy report form in Appendix 8.

11.4 Contact with the subject's other physicians

The investigator will determine whether any medical encounters outside of this study are being performed by the subject during the study. If the subject is being treated by another physician, the physician will be notified of the subject's participation in the study with the subject's consent. In addition, the investigator (subinvestigator) or a study collaborator will provide subjects with the study participation card, etc. and instruct subjects to present it when they visit other hospitals or departments in order to inform other physicians about subjects' participation in the study through subjects.

12. Subject Discontinuation Criteria and Procedures

12.1 Subject Discontinuation Criteria

The study will be discontinued if any of the following discontinuation criteria are met:.

(1) Subject's request for discontinuation
(2) The subject is found to be clearly ineligible for the study.
(3) The investigator or subinvestigator considers that continuation of the study is difficult because of adverse events, etc.
(4) The investigator or subinvestigator judges that it is inappropriate to continue the study because of worsening of the primary disease.
(5) Other cases where the investigator (subinvestigator) judges that the study should be discontinued.

[Rationale]

These criteria were set to ensure ethical conduct of the study and in consideration of subject safety.

12.2 Discontinuation Procedures

If the study is discontinued, the Investigator (or Subinvestigator) will take appropriate measures for the subject and perform the tests/observations specified for the time of discontinuation. The investigator or subinvestigator will promptly notify the sponsor of the discontinuation. The date of discontinuation is defined as the date when the investigator/subinvestigator decided to discontinue the study.

If the study is discontinued during the period of administration of investigational product, the investigator (subinvestigator) will perform the tests at discontinuation of the treatment period of investigational product by the next day after the last day of administration.

If the study is discontinued during the post-treatment observation period of investigational product, the investigator (subinvestigator) will perform the examination at discontinuation of the observation period within 8 days after the day of discontinuation.

Regardless of the timing of discontinuation, subjects will be evaluated for safety 3 months after onset wherever possible.

The investigator or subinvestigator will record the date of discontinuation and the reason for discontinuation in the case report form. In addition, if the subject is withdrawn from the study due to an adverse event, the name of the event leading to withdrawal will be recorded in the withdrawal section of the CRF.

For subjects for whom the specified observations and examinations at discontinuation could not be performed or subjects who did not visit the study site after discharge, follow-up investigation will be performed in writing (sealed letter) or by telephone, etc. to find out the reason and subsequent course, and the details will be recorded in the source documents, etc.

13. Statistical Analysis

13.1 Analysis Sets

Efficacy analyses will be performed on the Full Analysis Set (FAS). The primary endpoint will also be analyzed secondarily in the per protocol set (PPS). The safety analysis set will be used for safety analyses.

The analysis sets are defined below. The details of handling of subjects will be determined by the sponsor before data lock.

(1) Efficacy analysis set

1) FAS

The FAS will consist of all randomized subjects excluding the following subjects.

- Subjects without cerebral infarction
- Subjects who have never received investigational product
- Subjects with no efficacy data after randomization

2) PPS

The PPS is defined as the analysis set consisting of subjects in the FAS excluding the following subjects.

- Subjects who deviated from the inclusion criteria
- Subjects who met any of the exclusion criteria
- Subjects who met the criteria for prohibited concomitant drugs or therapies
- Subjects who received ≤ 80% of investigational product doses in the continuous intravenous infusion regimen or ≤ 80% of investigational product doses in the approved regimen after the start of treatment until the investigator (subinvestigator) judged that investigational product treatment would be completed

(2) Safety Analysis Set

The safety analysis set will consist of all randomized subjects excluding the following subjects.

- Subjects who have never received investigational product
- Subjects with no safety data after randomization

13.2 Data Handling

Data will be handled as follows except for matters determined at the case review meeting of the sponsor.

(1) Missing Definition

If measurement becomes impossible due to missing test data or problems with test samples, etc., the relevant item will be handled as missing.

(2) Handling of time point data in tabulation by time point

For tabulation at each measurement time point, data that meet the acceptable range defined in Section 9.1 will be adopted. If there are multiple data within the acceptable range, the one closest to the evaluation date will be adopted.

Deviations from the acceptable range and handling of other data, if necessary, will be determined by the sponsor prior to data lock and specified in the statistical analysis plan.

13.3 Statistical and Analytical Plans

13.3.1 Efficacy

(1) Analysis of the primary endpoint

1) Primary Analysis

Changes in NIHSS over 7 days after the onset (measured daily from baseline to Day 7) will be compared by a survival analysis with "NIHSS improvement by ≥ 4 points" at the evaluation time point as an event. The comparison between the H group and the control group will be performed first, then the comparison between the L group and the control group will be performed only if a statistically significant result is obtained. The definition of censoring will be specified in the statistical analysis plan. A stratified log-rank test stratified by randomization factors will be used for the test.

2) Secondary Analyses

As survival time analysis, between-group comparison will be performed using a Cox regression model with groups and allocation factors as covariates, and the hazard ratio, its 95% confidence interval, and p-value will be presented.

(2) Analysis of secondary endpoints

1) NIHSS

For NIHSS on Day4, Day7, Day10, Day14, Week 3, discharge, and Month 3, descriptive statistics, treatment differences, and their 95% confidence intervals will be calculated for each group.

2) mRS

For mRS at 3 weeks, at discharge, and at 3 months, the proportion of mRS 0 or 1 at each measurement time point and the between-group difference in the proportion and its 95% confidence interval will be calculated.

3) BI

For the total BI score (0~ 100) on Day14, Week 3, at discharge, and at 3 months, descriptive statistics, inter-group differences, and their 95% confidence intervals should be calculated.

In addition, the proportion will be categorized based on the BI score, and the proportion at each measurement time point and the between-group difference in the proportion and its 95% confidence interval will be calculated.

4) FIM

For the total FIM score (18~126 points) measured at Week 3, discharge, and Month 3, descriptive statistics, inter-group differences, and their 95% confidence intervals will be calculated.

Descriptive statistics and between-group differences with their 95% confidence intervals will be calculated for the scores for the motor (13~91 points) and cognitive (5~35 points) items.

5) Time to start rehabilitation

Descriptive statistics of each group (start date of rehabilitation - date of hospitalization) and

between-group differences with their 95% confidence intervals will be calculated.

6) Duration of hospitalization

Descriptive statistics and between-group differences in the duration of hospitalization (date of discharge - date of admission) and their 95% confidence intervals will be calculated for each group.

(3) Analysis of exploratory endpoints

[redacted]

13.3.2 Image Analysis

(1) Infarct focus volume

Descriptive statistics and between-group differences in infarct volume and their 95% confidence intervals will be calculated for each group.

(2) Degree of cerebral edema

Change in edema will be calculated, and descriptive statistics, treatment differences, and their 95% confidence intervals will be calculated for each group.

(3) Presence or absence of intracranial hemorrhage

The proportion of intracranial hemorrhage will be calculated by severity, and descriptive statistics, between-group differences, and their 95% confidence intervals will be calculated for each group.

13.3.3 Safety

The number and proportion of subjects with adverse events, adverse reactions, serious adverse events, and serious adverse reactions will be tabulated by SOC and PT for each group.

For each laboratory, vital sign, and ECG parameter, summary statistics (Mean, standard deviation, minimum, median, maximum) by treatment group and measurement time point, and summary statistics of differences from baseline will be presented.

For neurological examination, shift tables of changes from the onset to Day5 will be presented by group and measurement time point.

For urinalysis, shift tables of changes from baseline will be presented by group and measurement time point.

13.3.4 Significance Level and Confidence Interval

All tests will be two sided, with a level of significance set at 5%. The significance level of each test will be

set at 5% because a fixed order test method was adopted for the analysis of the primary endpoint in consideration of multiplicity. The confidence interval will be two-sided, and the confidence coefficient will be 95%.

13.4 Changes in the statistical analysis plan

If the statistical analysis plan described in this section is changed before data lock, the reason for the change will be described in the statistical analysis plan and the clinical study report. If the analytical method is changed or an additional analysis is performed after data lock, the reason will be described in the statistical analysis plan and the clinical study report to distinguish it from the results of the planned analysis.

14. Compliance with, Deviations from, or Changes in the Protocol

14.1 Agreement on and Compliance with the Protocol

Before agreeing with the sponsor on the protocol, the investigator must have a discussion with the sponsor based on the protocol provided by the sponsor, the latest version of Investigator's Brochure, and other necessary documents, and fully examine the ethical and scientific validity of conducting the study.

Based on the examination results, the investigator will agree with the sponsor on the contents of the protocol and CRF, and sign (or sign and seal) and date the agreement with the sponsor as evidence of agreement to comply with the protocol.

14.2 Protocol Deviations or Changes

The investigator (subinvestigator) must not deviate from or change the protocol without prior written agreement between the investigator and the sponsor and written approval of the IRB based on prior review. However, the Investigator (or Subinvestigator) may deviate from or change the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB.

In such cases, the investigator must submit the details of the deviation or change and the reason, as well as the draft revision of the protocol, if revision is appropriate, to the sponsor, the head of the study site, and the IRB as soon as possible to obtain their approval. At the same time, the investigator must obtain written approval from the head of the study site and written agreement from the sponsor.

The investigator must document all protocol deviations. Only for deviations from the protocol committed to eliminate immediate hazards to subjects or for other medically unavoidable reasons, the investigator will prepare a document describing the reason, immediately submit it to the sponsor and the head of the medical institution, and retain a copy.

The investigator will promptly submit reports to the sponsor, the head of the study site, and the institutional review board on any changes that may significantly affect the conduct of the study or increase risks to subjects.

15. Protocol Amendments

If the sponsor considers it necessary to change the protocol during the course of the study, the sponsor will revise the protocol. The sponsor will consult and obtain agreement from the investigator on the details of the amendment, then promptly notify the head of the study site in writing, and obtain approval from the IRB via the head of the study site.

If the head of the study site instructs to modify the protocol based on the opinion of the IRB, the sponsor will determine whether the modification is appropriate and revise the protocol if necessary. Upon discussion and agreement with the investigator on the details of the amendment, the investigator will promptly notify the head of the study site in writing and obtain the approval of the institutional review board via the head of the study site.

If any modifications are required after discussion with the investigator, the sponsor will determine whether the changes are appropriate and revise the protocol if necessary. After reaching an agreement with the investigator on the details of the amendment, the investigator will promptly notify the head of the study site in writing and obtain the approval of the institutional review board via the head of the study site.

16. Discontinuation or Suspension of the Study

(1) Criteria for Premature Termination or Suspension of the Study

If any of the following cases occurs, the sponsor will consider whether to continue the study at all study sites or some study sites.

1) Information concerning the quality, efficacy, and safety of investigational product or other information important for the proper conduct of the clinical trial becomes available.
2) When a change to the protocol is required and the site is not able to accommodate this.
3) The head of the study site issues an instruction to modify the protocol based on the opinion of the IRB, and the sponsor cannot accept it.
4) The head of the study site instructed to discontinue the study based on the judgment of the IRB.
5) The study site is in significant or continuous violation of GCP, this protocol, or the study contract.

(2) Early study termination or suspension by the sponsor

If the sponsor decides to discontinue or suspend the entire study, the sponsor will promptly notify the head of the study site and regulatory authorities of the decision and its reason in writing. When notified by the sponsor that the study will be discontinued or suspended, the head of the study site will promptly notify it and its detailed reason in writing to the investigator and the IRB.

When notified by the sponsor via the head of the study site of premature termination or suspension of the study, the investigator will promptly inform the subjects and ensure appropriate treatment.

The actions to be taken for subjects in the event of study discontinuation shall be in accordance with "12.2 Procedures for Discontinuation."

(3) Discontinuation or suspension of the study at the study site by the investigator or IRB

If the investigator discontinues or suspends the study at his/her discretion, the investigator will promptly

notify the head of the study site of the discontinuation or suspension and its detailed reason in writing. The head of the study site will promptly notify the sponsor and the IRB to that effect in writing.

If the IRB decides to discontinue or suspend the study, the head of the study site will be notified of the decision and its detailed reason in writing. The head of the study site will promptly notify the investigator and the sponsor of the fact in writing.

(4) Discontinuation of the study due to termination of the contract with the study site

If a study site is prematurely terminated by the sponsor due to serious or persistent violation of GCP, the protocol, or the study contract during the study period, the sponsor will promptly notify the regulatory authorities.

17. Matters related to case report forms

17.1 Forms of Case Report Forms, etc.

An EDC electronic case report form will be used in this study. The eCRF that is reviewed and electronically signed by the investigator will be handled as the original.

17.2 Identification of materials to be directly recorded in case report forms and to be source data

For the following items among the data recorded in the CRF, the records in the CRF will be used as source documents. However, if the relevant contents are clearly described in the medical record, etc., these documents will be used as source documents.

(1) Purpose of use of concomitant drugs and purpose of concomitant therapy

(2) Adverse events (Seriousness, severity, outcome, date of outcome, causal relationship with investigational product)

(3) Date and reason for discontinuation, adverse events leading to discontinuation

(4) Investigator's (subinvestigator's) comments

Any contents other than the above will be separately specified in writing by the sponsor and the investigator before the start of the study.

17.3 Precautions for Preparation of Case Report Form

The investigator (subinvestigator) or a study collaborator will prepare the case report form according to the following rules. Case report forms will be prepared in accordance with the "Manual for changes or corrections to case report forms" (*) provided separately by the sponsor.

*"Manual for changes or corrections of case report form": EDC operation manual, eCRF entry manual

(1) Prior to entry in the CRF, the sponsor will issue the user ID and password to the investigator (subinvestigator) and study collaborator and perform user management. The issued user ID and password will be managed individually by the investigator (subinvestigator) and study collaborator and will not be shared. Data will be entered by the investigator (subinvestigator) and study collaborator authorized to enter data.

(2) Case report forms will be prepared for patients to whom drugs are assigned.

(3) The investigator can record all items on the CRF. The subinvestigator can record all items in the case report form other than the electronic signature. Study collaborators may transcribe items not requiring medical judgment from source documents, such as transcription from medical records.

(4) If any change or correction is made to the CRF, the reason for the change or correction will be recorded as electronic information.

(5) The investigator will electronically sign the CRF on the EDC system after confirming that the CRF has been prepared accurately and completely and that audit trails and electronic signature information can be referred to.

(6) The investigator shall retain a copy of the case report form stored in a recording medium such as CD-R (an electronic case report form whose contents have been confirmed by the investigator and stored in PDF format). An environment in which the electronic case report form can be accessed (access right to the EDC system) shall be provided in place of a copy during the period after electronic signature until a recording medium such as CD-R is provided by the sponsor.

(7) If there is any inconsistency between the data recorded in the CRF and the source document, the investigator will prepare a record explaining the reason, submit it to the sponsor, and retain a copy.

17.4 Timing of Submission of Case Report Forms

The investigator (subinvestigator) will promptly prepare the case report form and submit it to the sponsor.

17.5 Handling of patient diary

The patient diary will be stored at the study site in accordance with the "21. (1) Records to be retained at the study site."

18. Direct Access to Source Documents, etc.

The investigator and the head of the study site will accept monitoring and audits by the sponsor and inspections by the IRB and regulatory authorities and ensure that all study-related documents are available for direct access at these times.

19. Quality Control and Quality Assurance of the Study

To maintain the quality and reliability of this study, the sponsor must perform "quality control of the study" and "quality assurance of the study" based on the Mitsubishi Tanabe Pharma Corporation GCP standard operating procedure. The study site and the investigator must cooperate with the sponsor in quality control and quality assurance of the study.

For quality control of the study, the monitor will perform direct access as appropriate to confirm that the study is being conducted in compliance with the procedure manual for study-related operations at the study site, the latest protocol, and GCP. They will also be asked to confirm that the accuracy and completeness of CRF entries reported by the investigator (subinvestigator) can be verified against study-related records such as source documents.

To ensure that the study is being conducted in compliance with the protocol and GCP, the auditor will conduct audits in accordance with the GCP standard operating procedure to confirm that quality control is being appropriately implemented.

20. Ethics

20.1 Ethical Conduct of the Study

This study must be conducted in compliance with the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, GCP, and the protocol, while paying attention to the ethical principles based on the Declaration of Helsinki.

20.2 Institutional Review Board

The IRB will review the conduct and continuation of the study from ethical, scientific, medical, and pharmaceutical viewpoints based on the contents of Investigator's Brochure, the protocol, and the informed consent form.

20.3 Subject Confidentiality

Subjects will be enrolled and identified in case report forms by subject identification codes, and persons involved in this study will maintain the confidentiality of subjects in direct access to source documents related to the conduct of the study, publication in medical journals, submission of documents to regulatory authorities, etc.

21. Retention of Records, etc.

(1) Records to be retained at the study site

The retention administrator appointed by the head of the study site shall retain study-related documents or records to be retained at the study site until the day specified in 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the study site should discuss how long and how to retain those documents with the sponsor.

If the sponsor has decided not to include the clinical data obtained in the clinical trial in the approval application, the sponsor will report it and the reason in writing to the head of the medical institution.

If the marketing approval of investigational product is obtained or if the sponsor decides to discontinue the development of Midi-chlorian without obtaining the approval, the sponsor will report it in writing to the head of the study site.

1) The day on which marketing approval of the said investigational product is obtained (In case of additional indication, the date of approval of partial change in marketing approval)(The day 3 years after the date of notification, if any, that the development has been discontinued or the clinical trial results will not be attached to the application for approval.)
2) The day 3 years after the date of premature termination or completion of the study

(2) Records to be retained by the sponsor

The sponsor will retain study-related documents and records to be retained by the sponsor until the day specified in 1) or 2) below, whichever comes later.

1) The day when 5 years have passed since the date of marketing approval of the said investigational product (In case of additional indication, the date of approval of partial change in marketing approval) (or the day

when 3 years have passed since the date of decision of development discontinuation if the development is discontinued) or the day of completion of reexamination

2) The day 3 years after the date of premature termination or completion of the study

22. Payments

Payments to subjects and study sites will be made in accordance with the contract or agreement between the study site and the sponsor.

23. Compensation for health injury and insurance

23.1 Compensation for Injury

If a subject suffers any health damage due to participation in this study, the sponsor will appropriately compensate according to the standard specified by the sponsor unless the causal relationship with the study is denied (Compensation consists of medical expenses < copayment portion >, medical allowance, and compensation payment.). In this case, the subject shall not bear the burden of proof of causal relationship, etc.

23.2 Insurance

The sponsor will take necessary measures, such as purchasing insurance, to ensure the fulfillment of the liability for compensation and indemnification for study-related health injury in subjects.

24. Publications

The information contained in this protocol is the property of the sponsor and will be provided to the persons involved in the study such as the investigator (subinvestigator) who conduct this study and the institutional review board, but must not be disclosed to any third party without written agreement of the sponsor except when it is necessary for the conduct of the study.

If persons involved in the study at the study site such as the investigator (subinvestigator) publish information obtained from the study externally such as to a professional academic conference, prior approval of the sponsor must be obtained.

The sponsor is free to use the information obtained from this study for the purpose of reporting to the regulatory authorities, proper use of drugs, marketing, etc.

25. Gene analysis test

For sites where blood samples for the genetic analysis study can be collected, specific procedures will be followed and the genetic analysis study will be performed as specified in this section.

25.1 Objectives

Obtaining knowledge of drug effects and the relationship between adverse events and genes is important in establishing safer and more pharmacodynamically evaluated therapies. In the future, genetic analysis may also be performed for MCI-186 in order to investigate individual differences in drug response related to effects and adverse events. Therefore, blood samples will be collected and DNA extract samples will be stored in this study.

25.2 Study Population

Subjects who consent to participate in this study and the genetic analysis study will be included.

25.3 Informed Consent

In cooperation with the sponsor, the investigator will prepare the informed consent form for the gene analysis study separately from the informed consent form for participation in the study itself.

The prepared and revised documents should be submitted to the sponsor and approved by the IRB.

Prior to blood sampling for the gene analysis study, the Investigator (or Subinvestigator) will provide subjects with the informed consent form for the gene analysis study, provide them with a full explanation of the study, and obtain their written voluntary consent to participate in the gene analysis study.

The investigator (subinvestigator) who explained the study and the subject will sign (or mark with a seal) and date the informed consent form, and provide the subject with a copy of the completed form. If a study collaborator has provided supplementary explanation, the study collaborator will also sign (or mark with a seal) and date the informed consent form.

Even if consent for the genetic analysis study is not obtained, participation/continuation in the study is allowed if consent for the study is obtained.

25.4 Handling of samples

The blood samples will be stored at a contract research organization for storage of blood samples for genetic analysis.

25.4.1 Date of blood collection

Approximately 8.5 mL of whole blood will be collected into a blood collection tube containing an anticoagulant once at any time point from the start of investigational product to the evaluation day 3 months after the onset.

25.4.2 Storage and Shipping Conditions

Blood samples will be stored frozen until shipment. Blood samples will be collected by the contract clinical laboratory and sent to the genetic analysis sample storage facility. The contract clinical laboratory will store the collected blood samples in a frozen state until they are sent to the genetic analysis sample storage facility, and send them on sufficient dry

ice. The genetic analysis sample storage facility will extract DNA from the transported blood samples and store the DNA extract collectively in the genetic sample storage cabinet.

25.4.3 Procedures for anonymization/coding, preparation and storage of correspondence table

The genetic analysis sample storage facility will anonymize the transported blood samples in a linkable fashion, assign a sample anonymization number different from the subject number, and store the correspondence table. For details such as the method of anonymization and preparation/storage of the correspondence table, follow the written procedures of the genetic analysis sample storage facility or the study protocol.

25.4.4 Sending a copy of the correspondence table

A copy of the correspondence table prepared by the genetic analysis sample storage facility will be sent to the sponsor after completion of storage of the final sample.

25.4.5 Storage Period of DNA Extract Samples

The DNA extract samples will be stored for no longer than 15 years after completion of the study.

25.4.6 Disposal of Blood and DNA Extract Samples

The blood residue after DNA extraction will be discarded according to the written procedures of the genetic analysis sample storage facility or the study protocol.

In principle, the DNA extract samples will be stored for the period specified in 25.4.5 after the completion of the study, and then will be disposed of by the genetic analysis sample storage facility according to the written procedures prepared after obtaining the confirmation of the sponsor's consent to disposal.

If a subject withdraws his/her consent for the genetic analysis study, his/her DNA extract sample or blood sample will be discarded immediately after anonymization of samples.

25.5 Implementation of genetic analysis

Samples obtained for the genetic analysis studies will only be used for pharmacodynamic assessment of MCI-186 and genetic analysis related to safety drug response. Genetic analysis will be performed when the sponsor judges it necessary to examine regardless of the duration of this study, and it may not be performed. If a study using these samples is to be started, a protocol containing the contents of the study will be newly prepared, and the report will be prepared separately from the clinical study report of this study.

25.6 Publication of Analysis Results and Disclosure to Subjects Who Provided Samples

25.6.1 Publication of Analysis Results and Disclosure to Subjects Who Provided Samples

If persons involved in the study at the study site such as the investigator (subinvestigator) publish information obtained from the gene analysis study externally such as to a professional academic conference, prior approval of the sponsor must be obtained. The sponsor may freely use the information obtained from the analysis for the purpose of reporting to the regulatory authorities, proper use of drugs, marketing, etc.

In principle, genetic information obtained from analyses in individual subjects who provide specimens will not be disclosed to the donors themselves when the evaluation has not been established (clinical significance is unclear).

25.6.2 Disposal of Personal Genetic Information

If it becomes necessary to discard the genetic information of a sample donor due to withdrawal of consent of a subject, etc., the gene information control manager appointed at the time of conducting the gene analysis study will delete the electronic data of the subject from the dedicated computer, etc. where they are stored. Paper information shall be disposed of in a state where it cannot be shredded, etc. However, if the results of a group analysis using personal data have already been obtained at the time of withdrawal of consent, the results of the group analysis will be used even after withdrawal of consent. If the research results are published in a paper, etc., it may not be possible to discard all the results. Details of disposal of genetic information will be in accordance with the separately prepared procedure or study protocol.

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Contact Information

[redacted]

[redacted]

[redacted]

FAX [redacted]

Clinical Promotion, Ikuyaku Division, Mitsubishi Tanabe Pharma Corporation

[redacted]

TEL [redacted]

FAX [redacted]

Contact at night/on holidays

During the night (17:30 to 9:00 the next morning) and on non-business days of the sponsor such as Saturdays, Sundays, holidays, and the year-end and New Year holidays

The following emergency contact center will receive emergency calls and connect you to the monitor.

Mitsubishi Tanabe Pharma Corporation Emergency Contact Center

[redacted] (Toll Free)

[redacted]

[redacted]

[redacted]