STUDY PROTOCOL

Protocol Number: MCI-186-J23

A Multi-Center, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Mild or Moderate Hepatic Impairment Compared to Subjects with Normal Hepatic Function

EudraCT Number:	Not applicable
IND Number:	Not applicable
Investigational Medicinal Product:	MCI-186
Development Phase:	Phase I
Sponsor:	Mitsubishi Tanabe Pharma Corporation 3-2-10,Dosho-machi, Chuo-ku, Osaka-shi, Osaka 541-8505, JAPAN
Protocol Version	05.01.00000
Protocol Date:	2 April 2018
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In-text Tables

SIGNATURE PAGE (SPONSOR'S RESPONSIBLE SIGNATORY)

Protocol Number: MCI-186-J23

A Multi-Center, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Mild or Moderate Hepatic Impairment Compared to Subjects with Normal Hepatic Function

The Protocol has been designed according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP), Japan-GCP and the Declaration of Helsinki (Fortaleza, Brazil, 2013). It has undergone both medical and scientific review by competent Sponsor personnel.

Sponsor Signatory:

[redacted] Date

[redacted]
Mitsubishi Tanabe Pharma Corporation
17-10, Nihonbashi-Koamicho, Chuo-ku, Tokyo,
103-8405, JAPAN

SIGNATURE PAGE (INVESTIGATOR)

Protocol Number: MCI-186-J23

A Multi-Center, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Mild or Moderate Hepatic Impairment Compared to Subjects with Normal Hepatic Function

I confirm that I have read this Protocol and understand its contents. I agree to fully comply with its requirements.

I agree to make no changes to the conduct of the study as defined by the Protocol without the prior authorisation of Mitsubishi Tanabe Pharma Corporation in the form of a Protocol Modification and the appropriate regulatory and Institutional Review Board approvals.

Address of Institution: _____

_____

_____

_____

Signed: _____

Print Name: _____

Title: _____

Date: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AIS	Acute Ischemic Stroke
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ALS	Amyotrophic Lateral Sclerosis
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
AUC_{0-last}	Area under the concentration-time curve from time zero to the last measurable concentration
[redacted]	[redacted]
BLQ	Below the limit of quantification
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CI	Confidence interval
CK	Creatine kinase
CL	Total clearance
[redacted]	[redacted]
C_{max}	Maximum observed concentration
CRF	Case Report Form
CRO	Contract Research Organisation
CS	Clinically significant
CSR	Clinical Study report
CT	Computed Tomography
CV	Coefficient of variation
CV%	Coefficient of variation percentage
DBP	Diastolic blood pressure
DCF	Data Clarification Form
ECG	Electrocardiogram
eCLcr	Estimated creatinine clearance
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Definition
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotrophin
HCVAb	Hepatitis C virus antibody
HDL-C	High density lipoprotein-cholesterol
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
Kel	Terminal elimination rate constant
LD_{50}	Lethal dose 50%
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein-cholesterol
LLOQ	Lower limit of quantification
LS mean	Least squares mean
MAD	Multiple ascending dose
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRT	Mean residence time
NCS	Not clinically significant
NOAEL	No observed adverse effect level
PK	Pharmacokinetic(s)
PP	Per Protocol
PPK	Population pharmacokinetics
QP	Qualified Person
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fridericia's formula
RBC	Red blood cells
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
[redacted]	[redacted]

Abbreviation	Definition
SD	Standard deviation
SI	International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Apparent elimination half-life in plasma
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization
[redacted]	[redacted]

PROTOCOL SYNOPSIS

Protocol number:	MCI-186-J23
Protocol title:	A Multi-Center, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Mild or Moderate Hepatic Impairment Compared to Subjects with Normal Hepatic Function
Sponsor:	Mitsubishi Tanabe Pharma Corporation 3-2-10,Dosho-machi, Chuo-ku, Osaka-shi, Osaka 541-8505, JAPAN
Development phase:	Phase I
Planned study period:	First subject enrolled: September 2016 Last subject last visit: August 2018
Indication:	Amyotrophic lateral sclerosis and acute ischaemic stroke in Japan
Investigational medicinal products (IMPs):	Product name : MCI-186 ampule Formulation : Injection Strength : 30 mg of edaravone in 1 ampule (20 mL) Storage : Store at room temperature
Treatment regimen:	Dose : 30 mg Route : Intravenous injection Frequency : Single dose One ampule (30 mg of edaravone) will be diluted with 100 mL of physiological saline, which will be administered intravenously over 60 minutes in the morning of Day 1.
Study duration:	Up to 30 days Day -21 to Day -2: screening Day -1: admission to unit Day 1: dosing Day 3: discharge from unit Day 7 (+2 days): follow-up visit
Objectives:	Primary Objective: • To assess the pharmacokinetics of MCI-186 after a single intravenous infusion of 30mg/hour in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function. Secondary Objective: • To investigate the safety and tolerability of MCI-186 in subjects with mild or moderate hepatic impairment and in subjects with normal hepatic function.
Study design:	This is multi-center, open-label, single dose study in male and female subjects with milde or moderate hepatic impairment, and normal hepatic function. The study will be conducted in the following three groups. Group 1: Subjects with mild hepatic impairment (Child-Pugh A) Group 2: Subjects with moderate hepatic impairment (Child-Pugh B)

	Group 3: Subjects with healthy normal hepatic function to match Group 1 and Group 2 for age, body weight, and gender
Planned number of subjects:	24 subjects will be enrolled to ensure 18 subjects complete the study. 8 subjects (including male and female subjects) will be allocated per group and at least 6 subjects will be completed and evaluable per group. Each group to contain a minimum of 2 subjects per gender. If possible, mixed male and female groups, split approx. 50% across groups but with a minimum of two females per group. (No analysis of the gender difference)
Subject population:	Male or female subjects with mild or moderate hepatic impairment and normal hepatic function.
Inclusion criteria:	**All subjects** 1. Male or female subjects age 20 to 75 years (both inclusive) at signature of the Informed Consent Form (ICF). 2. Able to provide written informed consent to participate in this study after reading the ICF, and after having the opportunity to discuss the study with the Investigator or designee, before any screening or study related procedures take place. 3. In the Investigator's opinion, subject is able to understand the nature of the study and any risks involved in participation, and willing to cooperate and comply with the Protocol restrictions and requirements. 4. A body weight of ≥45 kg in males or ≥40 kg in females and a body mass index (BMI) ranging from 18 to 30 kg/m^2 (inclusive) at Screening and Day -1. 5. Female subjects a) who are postmenopausal (absence of menses for one year or more and follicle stimulating hormone (FSH) >30 mIU/mL), or b) who are surgically sterilised, or c) who are congenital sterility, or d) who use an effective methods of birth control from the Screening or at least 2 weeks before Investigational Medicinal Product (IMP) administration (whichever is earlier) until 14 days after the last dose of IMP. 6. Male subjects (including those who have had a vasectomy) a) who agree to use an adequate contraception method (e.g., condom with spermicide or partner using effective contraception) and to not donate sperm until 14 days after the last dose of IMP. **Hepatic impaired subjects (in addition)** 7. A Child-Pugh score of 5 or 6 for subjects with mild hepatic impairment, and between 7 and 9, inclusive, for subjects with moderate hepatic impairment obtained during Screening period (i.e., within 21 days before IMP administration) and Day -1. A

	diagnosis of hepatic impairment due to parenchymal liver disease, which is confirmed and documented by medical history physical examination, and hepatic ultrasound, Computed Tomography (CT) scan, Magnetic Resonance Imaging (MRI), or liver biopsy. 8. Chronic (>6 months) and stable hepatic impairment defined as no clinically significant change in disease status at least 30 days before Screening, as documented by subject's recent medical history. 9. Acceptable clinical conditions in the opinion of the investigator on the basis of a physical examination, medical history, ECG, vital sign, and clinical laboratory test (biochemistry, haematology, coagulation and urinalysis) at Screening, Day -1 and pre-dose on Day 1. Subjects with stable mild chronic concurrent diseases, such as degenerative joint disease, controlled diabetes, hypertension or hyperlipidemia, etc. may be included. **Healthy subjects (in addition)** 10. Subject with normal hepatic function. 11. Good health and free from clinically significant illness or disease in the opinion of the investigator on the basis of a physical examination, medical history, ECG, vital sign, and clinical laboratory test (biochemistry, haematology, coagulation and urinalysis) at Screening, Day -1 and pre-dose on Day 1.
Exclusion criteria:	**All subjects** 1. Presence or history of severe allergy to food, or any medicinal product or relevant excipient that is of clinical significance. 2. Subjects were previously administered MCI-186. 3. As a result of the medical screening process, the Investigator considers the subject not suitable for the study. 4. Clinically significant abnormal ECG findings at Screening, Day -1 or before dosing as in the opinion of the Investigator. 5. Any other history or condition (surgical or medical) of disease which will increase the risk to the subject or will affect PK of the study drug or will otherwise influence the assessments to be made in this study in the opinion of the Investigator. 6. Positive urine drug screen (if not due to concomitant medication) or alcohol test at Screening and Day -1 7. History of drug abuse 8. Presence of alcohol abuse 9. Subjects regularly, or on average, drank more than 28 units (224 g as pure alcohol) for man or 21 units (168 g) for female of alcohol per week (e.g., 20 g is equivalent to 500 mL of beer, 22 g is equivalent to 180 mL of sake or 12 g is equivalent to 120 mL of wine) 10. Presence of active infection requiring antibiotics

	11. Positive test for human immunodeficiency virus (HIV) antigen/antibody 12. Donate blood more than 200 mL within 4 weeks, 400 mL within 16 weeks for female or 12 weeks for male, 600 mL within 52 weeks for female or 1000 mL within 52 weeks for male, respectively before providing a signed ICF 13. Donate plasma or platelet component within 2 weeks before providing a signed ICF 14. Participation in another trial within 12 weeks or 5 times the half-life of the drug whichever is longer before providing a signed ICF. For biologics, the minimum period is at least 24 weeks or the period of the pharmacodynamic effect, or 10 times the half-life of the drug, whichever is longer before providing a signed ICF. 15. Subject is currently taking non-permitted concomitant medication. The subjects with normal hepatic function are restricted from use of any concomitant medications unless discussed and agreed with the Sponsor. On-demand use of acetylsalicylic acid for mild analgesia or use of oral contraceptives is permitted. In subjects with hepatic insufficiency, the use of prescribed medications is permitted for hepatic or concomitant disease as described in the Protocol. 16. Not willing to abstain from consumption of caffeine, cola or tea from admission to the unit (Day -1) to discharge the unit (Day 3) 17. Uncontrolled, or untreated hypertension defined as a mean of 3 repeated measurements of systolic blood pressure (SBP)>160 mmHg and/or diastolic blood pressure (DBP)>100 mmHg. 18. Subjects have estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 as determined by the 3-variable Japanese equation 19. Any condition associated with dehydration 20. Female subjects a) who have a positive pregnancy test at the Screening and on Day -1. b) who are pregnant, lactating, or planning to become pregnant during the study. **<u>Hepatic impairment subject (in addition)</u>** 21. Subjects with severe ascites which will, in the opinion of the investigator, adversely affect the subject's ability to participate in the study. 22. Subjects with encephalopathy >grade 1 23. Subjects with sclerosing cholangitis. 24. Serum albumin <2.0 g/dL. 25. Haemoglobin <8 g/dL and prothrombin time (sec over control) >6 26. Start of any new medication or new any changes to a current dosage within 4 weeks before admission (Day -1).

	Healthy subject (in addition) 27. History or presence of any parenchymal hepatic disease 28. Positive test for hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb).
Endpoints:	**Primary Endpoints:** The following PK parameters of MCI-186 will be calculated in the study: • Peak drug concentration (C_{max}); • Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$); • Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}\infty}$); **Secondary Endpoints:** The following secondary endpoints will be evaluated during the study: PK parameters of MCI-186 • Half-life ($t_{½}$); [redacted]
Statistical methods:	**Sample Size Calculation** The planned sample size of six evaluable subjects per hepatic impairment subjects group and per healthy subjects group is not based on a power calculation, but is according to FDA guidance for hepatic impairment PK study.

	Pharmacokinetic Data Analysis The plasma concentrations of MCI-186 will be summarized with descriptive statistics by time-point and groups, respectively. The PK parameters will be calculated for MCI-186 and the sulfate conjugate. The PK parameters C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ will be log-transformed prior to statistical analysis. 90% confidence intervals for the ratios of the mean $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and C_{max} of MCI-186 between each impaired hepatic function group and the normal hepatic function group will be constructed using the estimated least squares means and intersubject variance from analysis of variance (ANOVA). **Safety Data Analysis** Where appropriate, continuous variables will be summarized descriptively, using the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. Treatment-emergent adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized in incidence tables by System Organ Class (SOC) and Preferred Term. Concomitant medication will be coded using the World Health Organisation (WHO) Drug Dictionary (DD). Versions of the dictionaries used will be documented in the Data Management Plan and SAP.

1 INTRODUCTION

1.1 Background

MCI-186 (non-proprietary name; edaravone) is a free radical-scavenger developed as a neuroprotectant by Mitsubishi Tanabe Pharma Corporation (the Sponsor). MCI-186 was first approved in 2001 in Japan, under the trade name of RADICUT®, for the treatment of acute ischemic stroke (AIS) using intravenous (IV) infusion of 30 mg MCI-186 administered over 30 minutes twice a day for up to 14 days of treatment. MCI-186 was also approved in Japan in June 2015, in South Korea in December 2015 and in the United States in May 2017 for the treatment of amyotrophic lateral sclerosis (ALS) based upon a series of clinical studies completed in Japan for ALS. The ALS dosing regimen is once a day IV infusion of 60 mg administered over 60 minutes following dosing cycles defined as follows: Cycle 1 consists of 14 consecutive treatment days followed by a 2-week drug-free period, all subsequent cycles consisting of 10 treatment days over 2 weeks followed by a 2-week drug-free period.

1.2 Nonclinical studies

MCI-186 inhibited vascular endothelial cell damage in vitro and, when intravenously administered to cerebral ischemic animals (rats), demonstrated such effects as inhibition of cerebral edema, protection from tissue damage, improvement of neurological symptoms, and inhibition of delayed neuronal death in vivo. MCI-186 also inhibited a decrease in inclined plane angle in females of mutant SOD transgenic rats. Moreover, MCI-186 also inhibited cerebral vasospasms in a canine subarachnoid haemorrhage model.

In safety pharmacology studies, [redacted]

[redacted]

Pharmacokinetic (PK) studies showed good correlation between dose and C_{max} or AUC in animals and human. MCI-186 is rapidly metabolized. The major metabolites are the glucuronide and the sulfate conjugates, and urinary excretion is the main metabolic pathway. *In vitro* studies suggested that the sulfate is deconjugated and then reconjugated to the glucuronide in the human kidney before excretion into urine. [redacted]

More detailed nonclinical data can be found in the Investigator's Brochure [1].

1.3 Clinical studies

[redacted]

A single-dose, Phase I study (0.2 to 2.0 mg/kg) in which intravenous infusion was performed for 40 minutes or 3 hours in Japanese healthy adult males and a repeated-dose study (1.0 mg/kg/day, 7 days) were conducted to investigate safety and PK. Although abnormal changes in laboratory data were reported in 2 subjects in the single-dose study, the values were found to have returned to normal in follow-up examinations. C_{max} or AUC was proportional to dose, half-life and urinary excretion rate were substantially constant regardless of dose, and there was no difference in pharmacokinetics between single dose and repeated doses (Table 1). Thus, there was no accumulation in plasma concentration after repeated doses.

[redacted]

In a repeated-dose study (0.5 mg/kg/30 min, twice daily, 2 days) in Japanese healthy male elderly and adult subjects, the PK parameters of unchanged MCI-186 and metabolites in plasma were substantially equal between the elderly and adult males (Table 2), and there was no change in urinary excretion. In addition, there was no difference in safety between the elderly and adult subjects and no particular clinically significant findings.

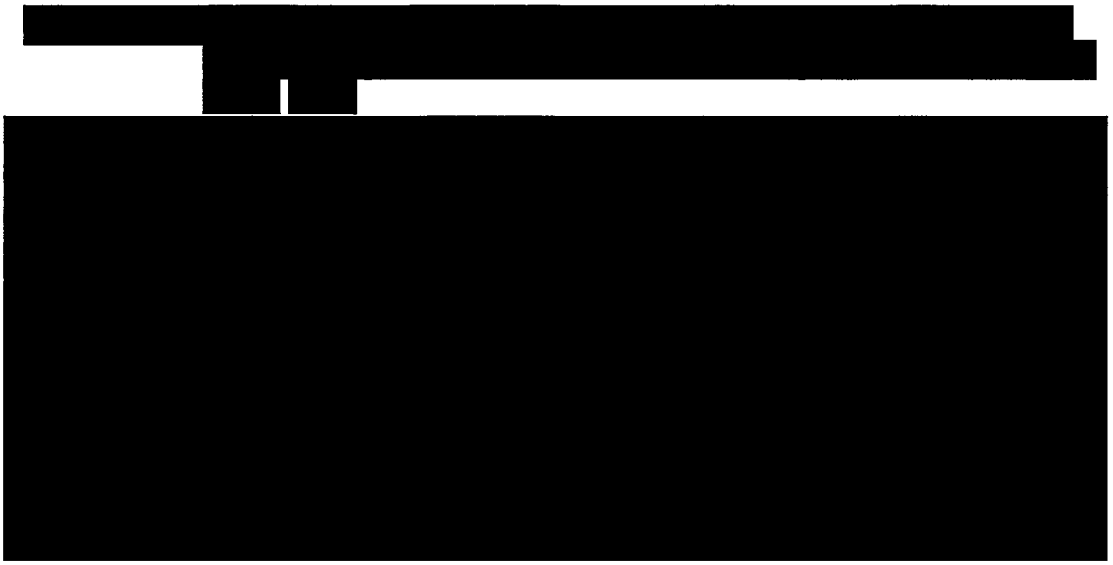
[redacted]

MCI-186 is metabolized into sulfate and glucuronide conjugates. In plasma, the sulfate was the predominant metabolite, and the concentration of the sulfate is higher than that of unchanged MCI-186. [redacted]

In addition to safety data in ALS clinical trials, 1.7 million patients in AIS and 1500 patients in ALS in Japan have been treated with MCI-186 showing acceptable safety profile. While hepatic and renal disorders were reported in post-marketing in AIS, these events were not observed as clinically significant findings in AIS and ALS clinical trial. The package insert in Japan presents that MCI-186 is contraindicated in patients with severe renal impairment and should be administrated with care in patients with hepatic impairment.

Detailed results of the Phase I clinical studies, AIS and ALS studies in Japan can be found in the Investigator's Brochure [1].

[redacted]



1.4 Overall rationale for the study

The FDA and European Medicines Agency (EMA) recommend a PK study in patients with impaired hepatic function when hepatic impairment is likely to mechanistically alter the PK of the drug and/or its active metabolites [3, 4].

Impaired hepatic function may result in increased concentration of unchanged MCI-186 in plasma and may affect the safety of MCI-186 when administered to a hepatic impaired patient. This may occur because MCI-186 is metabolized in the liver and kidney and mainly excreted via kidney into urine. Therefore, PK of MCI-186 will be investigated in subjects with hepatic impairment.

The tolerability of the dosing regiments 1.5 mg/kg/40 min and 2.0 mg/kg/3 hr were confirmed in a Phase I study (Table 1). In addition, hepatic and renal disorders were reported in post-marketing in AIS and the package insert in Japan presents that MCI-186 is contraindicated in patients with severe renal impairment and should be administrated with care in patients with hepatic impairment. Therefore, subjects with severe hepatic impairment will be excluded from this study. The planned dosing regimen for this study is a single dose of 30 mg MCI-186 intravenously administered over 60 minutes. The 30 mg dose is one-half of the approved daily therapeutic dosage for treatment of AIS or ALS.

[redacted]

Hishida [5] analysed 207 patients who had been reported as having developed renal disorders after treatment with MCI-186 in its post-marketed clinical use data. Hishida reported that MCI-186 was closely involved in renal disorder onset in 8.2% of patients and 65.2% of patients who developed renal disorders after treatment with MCI-186 were complicated by the severe deterioration of systemic status (e.g., severe infection and decreased blood pressure) which could cause renal disorders. The majority of patients who were treated with MCI-186 were elderly with AIS. These cases were frequently further complicated by the severe deterioration of systemic status. In addition, Hishida also reported risk factors for the non-recovery renal function and for death after treatment of MCI-186. The presence of severe infection and the implementation of blood purification were selected as possible risk factors for the non-recovery of renal function and four factors including advanced age (≥80 years), increased blood urea nitrogen (BUN) at discontinuation of MCI-186, presence of severe infection, and administration of antibiotics were selected as possible risk factors for death.

Hirano [6] investigated 123 patients with a verified episode of liver injury among 132 patients with serious liver injury that had been reported attributable to MCI-186. The number of patients with "MCI-186 related liver injury" was considered to be 25 (20.3%). Among 123 evaluated patients, 104 met the criteria for "evident liver injury" using modified Hy's Law. Of these 104 patients, 86 patients (82.7%) discontinued administration of MCI-186 after the onset of liver injury. The recovery rate in patients who discontinued MCI-186 administration (86 patients) was 62.8% (54/86 patients); among them, the recovery rate in patients who had MCI-186 related liver injury (17 patients) was 100% (17/17 patients). The following five factors were used as explanatory variables that are considered to affect prognosis: "advanced age (≥80 years)", "complications (hypertension, ischemic heart disease, atrial fibrillation, and heart failure)", "severe infections", "severe liver injury", and "continued administration of MCI-186 after the onset of liver injury". As a result, the model was refined until it included only two predictors: "advanced age (≥80 years)" and "severe infections".

Therefore, subjects with severe hepatic impairment who are aged > 75 years or present active infection requiring antibiotics will be excluded from this study and BUN and other renal and hepatic function parameters, such as creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and creatinine kinase (CK), red blood cell (RBC) count and platelet count, will be monitored during the study.

This study follows the recommendations given in the FDA and EMA guidelines for pharmacokinetics in subjects with impaired hepatic function [3, 4].

1.5 Rationale for treatment regimen

The AIS dosing regimen is twice a day IV infusion of 30 mg administered over 30 minutes for up to 14 days. [redacted] The ALS dosing regimen is once a day

IV infusion of 60 mg administered over 60 minutes for 14 days or 10 treatment days over 2 weeks followed by a 2-week drug-free period. [redacted] [2].

The dosing regimen in this study is a single dose of 30 mg MCI-186 intravenously administered over 60 minutes. The Sponsor set the 30 mg, one-half of the approved daily therapeutic dosage for treatment of AIS or ALS, to ensure the subjects' safety because the alteration of the PK profiles associated with the hepatic impairment is unclear. [redacted] [2].

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

2.1.1 Primary objective(s)

The primary objective of this study is to assess the pharmacokinetics of MCI-186 after a single intravenous infusion of 30 mg over 60 min in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function.

2.1.2 Secondary objectives

The secondary objective of this study is to investigate the safety and tolerability of MCI-186 in subjects with mild or moderate hepatic impairment and in subjects with normal hepatic function.

2.2 Study endpoints

2.2.1 Primary endpoint(s)

The following primary PK parameters of MCI-186 will be calculated in the study:

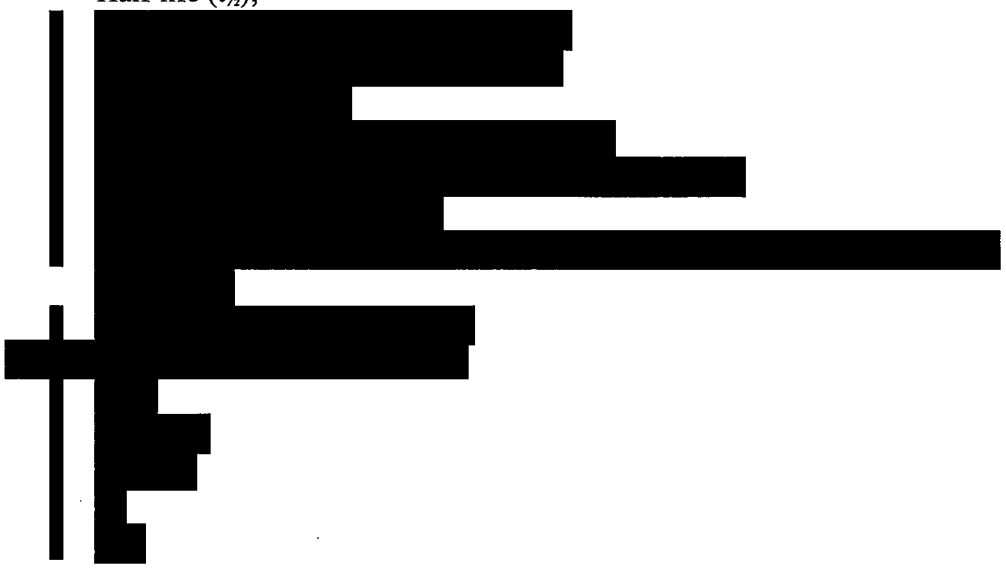
- Peak drug concentration (C_{max});
- Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$);
- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}\infty}$);

2.2.2 Secondary endpoints

The following secondary endpoints will be evaluated during the study:

PK parameters of MCI-186

- Half-life ($t_{½}$);



2.2.3 Exploratory endpoints

Not applicable in the study.

3 STUDY DESIGN

3.1 Overall study design

This is a Phase I, multi-center, open-label, single-dose study to evaluate the pharmacokinetics of MCI-186 in male or female subjects with mild hepatic impairment (Group 1, n = 8), moderate hepatic impairment (Group 2, n = 8) and normal hepatic function (Group 3, n=8) defined using the Child-Pugh classification (subjects with hepatic impairment only). Subjects may be replaced or additional subjects may be enrolled to ensure a minimum threshold of 6 completing and evaluable subjects per group based on the Child-Pugh classification (subjects with hepatic impairment only) at Day -1.

- Group 1: Subjects with mild hepatic impairment (Child-Pugh total score of 5 or 6)
- Group 2: Subjects with moderate hepatic impairment (Child-Pugh total score of 7 to 9)
- Group 3: Subjects with healthy normal hepatic function to match Group 1 and Group 2 for age, body weight, and gender

Order of Subject Enrollment

The control group (Group 3) will be enrolled once all hepatic impairment subjects (Group 1 and Group 2) will have been enrolled and will be matched with the hepatic impairment population with respect to age, gender and body weight. Age and body weight ranges must overlap between subjects with hepatic impairment and matched healthy subjects. After inclusion of all hepatic impaired subjects, the arithmetic mean and the 95% confidence interval of age and body weight at Day -1 will be determined. The group of healthy subjects will include subjects within the 95% confidence interval of the respective parameter. Each group to contain a minimum of 2 subjects per gender. If possible, mixed male and female groups, split approximately 50% across groups but with a minimum of two females per group (No analysis of the gender difference).

The subjects with mild hepatic impairment will be treated first. The second subject with mild hepatic impairment will not be treated until the completion of review for safety and PK profile in the first treated subject. [redacted]

Three subjects with mild hepatic impairment will be treated, and then the investigator and the Sponsor will assess the safety and PK results in these three subjects until after the end of trial (Day 7). A safety and PK review will be performed by the investigator and the Sponsor including the Medical advisor. The safety report will be compiled by the investigator, and the PK report will be compiled by [redacted]. The Sponsor will calculate C_{max} and AUC for the three subjects, against predicted C_{max} and AUC. The investigator and the Sponsor will decide together if subjects with moderate hepatic impairment may be included. Progression to treatment of subjects with moderate hepatic impairment

(Group 2) will not occur until this safety and PK review has been performed and approval is recorded by the investigator and the Sponsor.

The first subjects with moderate hepatic impairment will be assessed the safety and PK profile by the Investigator and the Sponsor. The second subject with moderate hepatic impairment will not be treated until the completion of review for safety and PK profile in the first treated subject. [redacted]

If there are significant safety concerns, the study may be stopped as described in Section 4.5.

Study Periods and Duration of Study

The study consists of

- A screening period (Day -21 to Day -2)
- A treatment hospitalization period (Day-1 to Day 3) with single intravenous infusion of 30 mg MCI-186 over 60 min on Day 1 and PK blood sampling until 48 hr post dose. All subjects will be confined to the study center from Day -1 to Day 3. Safety assessments will be performed until discharge.
- A follow-up period (Day 7 +2 days)
  An end of trial examination will be performed.

The duration of participation for the individual subject is expected to be up to 30 days.

3.2 Rationale for study design

This is a Phase I, multi-center, open-label, single-dose study. Blinding will not be used because the primary endpoint, the assessment of specified pharmacokinetic parameters, is not subject to bias from the participants or observers.

Both males and females (with a minimum of two subjects per gender in each group) will be included into the study. A gender effect will not be investigated.

Hepatic function of the subjects will be scored and classified using the Child-Pugh classification in accord with FDA and EMA guidance [3, 4].

The study design, including the chosen endpoints, follows the FDA and EMA recommendations for evaluating the effect of impaired hepatic function on pharmacokinetics. It is considered appropriate design for the clinical evaluation of the pharmacokinetics, safety, and tolerability of MCI-186 in this subpopulation of special interest.

3.2.1 Risk:benefit statement

[redacted]

1.7 million patients in AIS and 1500 patients in ALS in Japan have been treated with MCI-186 showing acceptable safety profile. While hepatic and renal disorders were reported in post-

marketing in AIS, these events were not observed as clinically significant findings in AIS and ALS clinical trial. The package insert in Japan presents that MCI-186 is contraindicated in patients with severe renal impairment and should be administrated with care in patients with hepatic impairment.

Therefore, as described in Section 1.4, severe hepatic impairment subjects as well as the following high risk subjects [5, 6] are excluded; subjects 1) who are advanced age (> 75 years) or 2) who present severe infection. In addition, the dosing regimen in this study is single dose of 30 mg MCI-186 intravenously administered over 60 minutes. 30 mg is one-half of the approved daily therapeutic dosage for treatment of AIS or ALS.

Furthermore, this Protocol includes frequent assessment of clinical and laboratory parameters including BUN, creatinine, AST, ALT, LDH and CK, RBC count and platelet count. The study will be conducted in stepwise. Subjects with moderate hepatic impairment will only be included after the safety and PK are assessed in three subjects with mild hepatic impairment. The study will be conducted at a study center specialized in conducting studies in subjects with hepatic impairment.

This is a PK study in healthy subjects and subjects with hepatic impairment. There are no direct benefits to the subject through participation in this study. However, they and other patients may benefit in future because the results of this study may guide appropriate use of MCI-186 ultimately in the drug labeling.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

The Sponsor does not operate a Protocol waiver (i.e., approval for prospective protocol deviations) for eligibility criteria.

4.1 Number of subjects

A total of 24 subjects will be enrolled to ensure 18 subjects complete the study.

4.2 Recruitment methods

Subjects with hepatic impairment will be recruited from those patients already attending clinics for the treatment of hepatic function or may be identified from a review of relevant databases. Matched healthy subjects will be recruited from a database of volunteers at the study center or other sites. All recruitment material will be approved by the Institutional Review Board (IRB) prior to implementation.

4.3 Inclusion criteria

A subject will be eligible for enrolment in the study if ALL of the following criteria apply:

All subjects

1. Male or female subjects age 20 to 75 years (both inclusive) at signature of the Informed Consent Form (ICF).
2. Able to provide written informed consent to participate in this study after reading the ICF, and after having the opportunity to discuss the study with the Investigator or designee, before any screening or study related procedures take place.
3. In the Investigator's opinion, subject is able to understand the nature of the study and any risks involved in participation, and willing to cooperate and comply with the Protocol restrictions and requirements.
4. A body weight of ≥45 kg in males or ≥40 kg in females and a body mass index (BMI) ranging from 18 to 30 kg/m^2 (inclusive) at Screening and Day -1.
5. Female subjects
   a) who are postmenopausal (absence of menses for one year or more and follicle stimulating hormone (FSH) >30 mIU/mL), or
   b) who are surgically sterilised, or
   c) who are congenital sterility, or
   d) who use an effective methods of birth control from the Screening or at least 2 weeks before Investigational Medicinal Product (IMP) administration (whichever is earlier) until 14 days after the last dose of IMP.
6. Male subjects (including those who have had a vasectomy)
   a) who agree to use an adequate contraception method (e.g., condom with spermicide or partner using effective contraception) and to not donate sperm until 14 days after the last dose of IMP.

Hepatic impaired subjects (in addition)

7. A Child-Pugh score of 5 or 6 for subjects with mild hepatic impairment, and between 7 and 9, inclusive, for subjects with moderate hepatic impairment obtained during Screening period (i.e., within 21 days before IMP administration) and Day -1. A diagnosis of hepatic impairment due to parenchymal liver disease, which is confirmed

and documented by medical history, physical examination, hepatic ultrasound, Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI), and/or liver biopsy.

8. Chronic (>6 months) and stable hepatic impairment defined as no clinically significant change in disease status at least 30 days before Screening, as documented by subject's recent medical history.
9. Acceptable clinical conditions in the opinion of the investigator on the basis of a physical examination, medical history, ECG, vital sign, and clinical laboratory test (biochemistry, haematology, coagulation and urinalysis) at Screening, Day -1 and pre-dose on Day 1. Subjects with stable mild chronic concurrent diseases, such as degenerative joint disease, controlled diabetes, hypertension or hyperlipidemia, etc. may be included.

Healthy subjects (in addition)

10. Subject with normal hepatic function.
11. Good health and free from clinically significant illness or disease in the opinion of the investigator on the basis of a physical examination, medical history, ECG, vital sign, and clinical laboratory test (biochemistry, haematology, coagulation and urinalysis) at Screening, Day -1 and pre-dose on Day 1.

4.4 Exclusion criteria

A subject will NOT be eligible for this study if ANY of the following criteria apply:

All subjects

1. Presence or history of severe allergy to food, or any medicinal product or relevant excipient that is of clinical significance.
2. Subjects were previously administered MCI-186.
3. As a result of the medical screening process, the Investigator considers the subject not suitable for the study.
4. Clinically significant abnormal ECG findings at Screening, Day -1 or before dosing as in the opinion of the Investigator.
5. Any other history or condition (surgical or medical) of disease which will increase the risk to the subject or will affect PK of the study drug or will otherwise influence the assessments to be made in this study in the opinion of the Investigator.
6. Positive urine drug screen (if not due to concomitant medication) or alcohol test at Screening and Day -1
7. History of drug abuse
8. Presence of alcohol abuse
9. Subjects regularly, or on average, drank more than 28 units (224 g as pure alcohol) for man or 21 units (168 g) for female of alcohol per week (e.g., 20 g is equivalent to 500 mL of beer, 22 g is equivalent to 180 mL of sake or 12 g is equivalent to 120 mL of wine)
10. Presence of active infection requiring antibiotics
11. Positive test for human immunodeficiency virus (HIV) antigen/antibody
12. Donate blood more than 200 mL within 4 weeks, 400 mL within 16 weeks for female or 12 weeks for male, 600 mL within 52 weeks for female or 1000 mL within 52 weeks for male, respectively before providing a signed ICF
13. Donate plasma or platelet component within 2 weeks before providing a signed ICF
14. Participation in another trial within 12 weeks or 5 times the half-life of the drug whichever is longer before providing a signed ICF. For biologics, the minimum period is

at least 24 weeks or the period of the pharmacodynamic effect, or 10 times the half-life of the drug, whichever is longer before providing a signed ICF.

15. Subject is currently taking non-permitted concomitant medication. The subjects with normal hepatic function are restricted from use of any concomitant medications unless discussed and agreed with the Sponsor. On-demand use of acetylsalicylic acid for mild analgesia or use of oral contraceptives is permitted. In subjects with hepatic insufficiency, the use of prescribed medications is permitted for hepatic or concomitant disease as described in Attachment 3.
16. Not willing to abstain from consumption of caffeine, cola or tea from admission to the unit (Day -1) to discharge the unit (Day 3).
17. Uncontrolled, or untreated hypertension defined as a mean of 3 repeated measurements of systolic blood pressure (SBP)>160 mmHg and/or diastolic blood pressure (DBP)>100 mmHg.
18. Subjects have estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 as determined by the 3-variable Japanese equation
19. Any condition associated with dehydration
20. Female subjects
    a) who have a positive pregnancy test at the Screening and on Day -1.
    b) who are pregnant, lactating, or planning to become pregnant during the study.

Hepatic impairment subjects (in addition)

21. Subjects with severe ascites which will, in the opinion of the investigator, adversely affect the subject's ability to participate in the study.
22. Subjects with encephalopathy >grade 1.
23. Subjects with sclerosing cholangitis.
24. Serum albumin <2.0 g/dL.
25. Haemoglobin <8 g/dL and prothrombin time (sec over control) >6.
26. Start of any new medication or new any changes to a current dosage within 4 weeks before admission (Day -1).

Healthy subjects (in addition)

27. History or presence of any parenchymal hepatic disease
28. Positive test for hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb).

4.5 Withdrawal of individual subjects

A subject will be withdrawn if ANY of the following criteria are met:

- The subject wishes to withdraw from further participation
- The subject is significantly noncompliant with the Protocol
- The subjects is discontinued due to safety reason; continuing in the study would be detrimental to the subject's safety in the opinion of the Investigator, such as
    - The subject experiences intolerable AEs or SAEs
    - The subject has clinically significant changes in safety parameters at any of the post-dose time points, as confirmed with a repeat assessment performed as soon as possible after the initial out-of-range result

In addition, a subject may be withdrawn at any time for any reason other than those listed here.

If a subject is discontinued prematurely from the study, the date the subject is withdrawn from the study and the reason for withdrawal will be recorded on the CRF.

In case of withdrawal of a subject, the Follow-up Visit assessments should be performed, as far as possible (Section 5.2.3).

Any withdrawal due to an AE or for any safety reason should always be considered serious.

Any unresolved AE or SAE will be followed up according to Section 8.9.

In the event that a subject elects not to return to the study center for the end of study visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the CRF. The study center personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required end of study assessments.

Subjects withdrawn for non-treatment-related reasons may be replaced at the discretion of the Sponsor and Investigator. Replacement subjects will receive the treatments intended for the withdrawn subject.

Criteria for amendment of dose in subjects with mild hepatic impairment (Group 1)

The subjects with mild hepatic impairment will be treated first. The second subject with mild hepatic impairment will not be treated until the completion of review for safety and PK profile in the first treated subject by the Sponsor and the Investigator. [redacted]

Procedure and criteria for starting treatment of subjects with moderate hepatic impairment (Group 2)

Three subjects with mild hepatic impairment will be treated, and then the investigator and the Sponsor will assess the safety and PK results in these three subjects until after the end of trial (Day 7). A safety and PK review will be performed by the investigator and the Sponsor including the Medical advisor. The safety report will be compiled by the investigator, and the PK report will be compiled by [redacted]. The Sponsor will calculate C_{max} and AUC for the three subjects, against predicted C_{max} and AUC. The investigator and the Sponsor will decide together, if there are no safety and PK concerns in all three subjects with mild hepatic impairment, subjects with moderate hepatic impairment may be included. Progression to treatment of subjects with moderate hepatic impairment will not occur until this safety and PK review has been performed and approval is recorded by the investigator and the Sponsor.

Detailed procedure is described in a separate document.

If any of the following criteria are fulfilled, progression to treatment of subjects with moderate hepatic impairment will be temporarily stopped.

- ≥2 subjects in the three subjects have severe or serious IMP-related AEs, or

- ≥2 subjects in the three subjects have ALT or AST >3 × baseline value in conjunction with elevated total bilirubin >2 × baseline value at any point after treatment, or
- ≥2 subjects in the three subjects have ALT or AST >3 × baseline value with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%), or
- ≥2 subjects in the three subjects have creatinine > 1.5 × baseline value

[redacted]

Criteria for amendment of dose in subjects with moderate hepatic impairment (Group 2)

The first subjects with moderate hepatic impairment will be assessed the safety and PK profile by the Investigator and the Sponsor. The second subject with moderate hepatic impairment will not be treated until the completion of review for safety and PK profile in the first treated subject by the Sponsor and the Investigator. [redacted]

If there are significant safety concerns, the study may be stopped.

4.6 Lifestyle restrictions

Subjects will be advised that they must adhere to the following restrictions:

4.6.1 Attendance

- Availability to attend visits according to the Protocol.
- Availability for overnight stays in the study center from Day -1 to Day 3.

4.6.2 Alcohol restrictions

- Subjects should refrain from consuming food or drink containing alcohol in the 24 hours before each visit and whilst confined to the study center.
- Subjects should avoid excessive consumption (>16 g as pure alcohol per day) of food or drink containing alcohol at all other times from the Screening Visit until the Follow-up assessment.

4.6.3 Xanthines

- Subjects should refrain from consuming food or drink containing caffeine and methylxanthine (e.g., coffee, tea, cola, energy drinks or chocolates) in the study center from Day -1 to Day 3, and from an awakening of the day of the Screening or Follow-up Visits until end of each examination.
- Subjects should avoid excessive consumption (>5 cups of coffee or equivalent per day) of food or drink containing caffeine and methylxanthine (*e.g.*, coffee, tea, cola, energy drinks or chocolates) at all other times from the Screening Visit until the Follow-up assessment.

4.6.4 Smoking

No smoking or using tobacco- or nicotine-containing products (snuff, chewing tobacco, cigarettes, cigars, pipes, e-cigarettes or nicotine replacement products) in the study center from Day -1 to Day 3, and from an awakening of the day of the Screening or Follow-up Visits until end of each examination.

4.6.5 Contraception

Female subjects of child-bearing potential* must be willing and able to practice birth control for the duration of the study, from the Screening or at least 2 weeks before IMP administration (whichever is earlier) until 14 days after the last dose of IMP. Male subjects must be willing and able to practice birth control for the duration of the study, from the time of the first dose of IMP until 14 days after the last dose of IMP.

- **Female subjects** must be willing to use a highly effective method of birth control (*i.e.*, contraceptive measure with a failure rate of <1% per year), in conjunction with male barrier contraception (*i.e.*, male condom with spermicide). Highly effective methods of contraception include:
  - Placement of an intrauterine device.
  - Established use of oral hormonal methods of contraception associated with inhibition of ovulation.
  - Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). (For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.)
  - Bilateral tubal ligation.
- **Male subjects** with partners of child-bearing potential must use a barrier method of contraception (*i.e.*, male condom with spermicide) in addition to a second method of acceptable contraception used by their female partners. In addition to the list of highly effective contraception methods above, other acceptable methods of contraception include:
  - Diaphragm with spermicide.

  Male subjects must not donate sperm for the duration of the study, from the time of the first dose of IMP until 14 days after the last dose of IMP.

*Note: Women are considered to be of child-bearing potential unless they meet one of the following criteria as documented by the Investigator:

- Post-menopausal for at least 1 year, confirmed by follicle stimulating hormone (FSH) assessment (>30 mIU/mL).
- Hysterectomy, bilateral oophorectomy or salpingectomy.
- Congenital sterility.

4.6.6 Diet

- While confined to the study center, subjects will receive standardized meals at scheduled times.
- Subjects should have a breakfast at Day 1 after the pre-dose assessment including PK blood sampling and at least 30 min before starting of IMP administration.

- Lunch at Day 1 (dosing day) will be provided at approximately 13:00 (i.e., after PK blood collection of 3 hours post-dose).
- Subjects will be required to fast (except for water) at least 5 hours prior to routine safety blood sampling.
- Subjects should refrain from ingesting food or drink containing poppy seeds in the 72 hours before the Screening Visit and from 72 hours before the Check-in (Day -1).

4.6.7 Physical activity restrictions

- Must not participate in heavy physical training or excessive exercise (eg, long distance running, weight lifting or any physical activity to which the subject is not accustomed) from 7 days before first dose of IMP, during the study and until the final follow-up assessment.

4.6.8 Blood donation

- Subjects must not have donated blood more than 200 mL within 4 weeks, 400 mL within 16 weeks for female or 12 weeks for male, 600 mL within 52 weeks for female or 1000 mL within 52 weeks for male, respectively before providing a signed ICF
- Subjects must not have donated plasma or platelet component within 2 weeks before providing a signed ICF
- Subjects must agree not to donate blood for 3 months after the last follow-up assessment

5 STUDY PLAN

Study assessments are summarized in the Time and events schedule (Table 5), and the study procedures are presented in Section 6. Any deviation from study procedures should be noted in the source documents and should be reported to the Sponsor immediately.

Table 5 Time and events schedule

Study Period	**Screening**	**Treatment Hospitalization**																**Follow -up**
Study Day	**-21 to -2**	**-1**	**1**													**2**	**3**	**7 (+2)**
[redacted]																		
Informed consent	X																	
Confinement		←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	
Outpatient	X																	X
Inclusion/exclusion criteria	X	X	X															
Demography & medical history	X																	
Physical examination	X	X	X													X	X	X
Weight	X	X														X	X	X
Height	X																	
BMI	X	X																
Vital signs	X	X	X													X	X	X
12-lead ECG	X	X	X													X	X	X
Urine drugs of abuse & breath alcohol test	X	X																
Haematology, biochemistry, coagulation & urinalysis	X	X														X	X	X
eGFR	X	X														X	X	X
Hepatitis B &C and HIV	X																	
Pregnancy test in female	X	X																X
Protein binding blood sampling		X																
IMP administration				←	—	→												
[redacted]																		
AE and concomitant medications	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→

5.1 Subject informed consent

Prior to performing any study procedures, the Investigator (or subinvestigator) will ensure that the subject is given full and adequate oral and written information about the study and the subject must sign the ICF, as described in Section 11.2.1.

5.2 Description of study phases

5.2.1 Screening period (Day -21 to Day -2)

Screening assessments will be performed from Day -21 to Day -2. There may be more than one Screening Visit.

Written informed consent will be obtained before any screening procedures are performed. The information recorded for all subjects, regardless of their suitability for the study, will be retained, and archived.

The following assessments will be performed (refer to the Time and events schedule [Table 5] for further details):

- Written informed consent
- Verify inclusion/exclusion criteria
- Medical history
- Demography
- Physical examination (including height, body weight and BMI)
- 12-lead ECG
- Vital signs (including supine blood pressure, pulse rate and infra-axillary body temperature)
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis; serology[HBsAg, HCVAb, HIV antigen/antibodies]; screening for drugs of abuse and alcohol; pregnancy test and FSH for females only)
- Degree of hepatic impairment by Child –Pugh classification in subjects with hepatic impairment (Group 1 and 2)
- eGFR by 3-variable Japanese equation
- AE, and prior and concomitant medication recording

Re-screening will be allowed once if the subjects will agree to perform re-screening in ICF, except for subjects who will have received the study drug. A new written informed consent will not be necessary. Re-screening will be performed within 3 months after first Screening. If re-screening will be performed within 20 days between the first screening and Day -1 (admission to the study center), only deviant parameters will be re-measured. Results of the screening assessment will be replaced with a latest assessment.

5.2.2 Treatment hospitalization period (Day -1 to Day 3)

Subjects who successfully complete screening will return to the study center in the morning of Day -1 and will remain on-site until Day 3. Inclusion and exclusion criteria will be reviewed to confirm eligibility on admission (Day -1) and Day 1 pre-dose. Eligible subjects will proceed to dosing.

5.2.2.1 Baseline phase (Day -1 to Day 1 [pre-dose])

The following procedures will be performed on Day -1 (refer to the Time and events schedule [Table 5] for further details):

- Verify inclusion/exclusion criteria
- Physical examination (including body weight and BMI)
- 12-lead ECG
- Vital signs (including supine blood pressure, pulse rate and infra-axillary body temperature)
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis; screening for drugs of abuse and alcohol; pregnancy test for females only)
- Degree of hepatic impairment by Child –Pugh classification in subjects with hepatic impairment (Group 1 and 2)
- eGFR
- Blood sampling for protein binding
- AE and concomitant medication

Re-assessment of Day -1 will be allowed once if the subjects will be agree to perform the re-assessment in ICF, except for subjects who will have re-screening or have received the study drug. A new written informed consent will not be necessary. Re-assessment will be performed within 20 days between the screening and rescheduled Day -1. Only deviant parameters will be re-measured. Results of the Day -1 assessment will be replaced with a latest assessment.

The following procedures will be performed at pre-dose on Day 1 (refer to the Time and events schedule [Table 5] for further details):

- Verify inclusion/exclusion criteria
- Physical examination
- 12-lead ECG
- Vital signs (including supine blood pressure, pulse rate and infra-axillary body temperature)
- Blood sampling for PK analysis
- AE and concomitant medication recording

5.2.2.2 Treatment phase (Day 1 to Day 3)

Only subjects meeting all the inclusion and exclusion criteria and who are suitable for the trial, will be included into the treatment phase.

A single IV infusion of 30 mg MCI-186 will be administered over 60 min on Day 1.

The following assessments will be performed during the treatment phase (refer to the Time and events schedule [Table 5] for further details):

- Physical examination (including body weight on Day 2 and Day 3)
- 12-lead ECG
- Vital signs (including supine blood pressure, pulse rate and infra-axillary body temperature)
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis)
- eGFR
- Blood sampling for PK analysis
- AE and concomitant medication recording

5.2.3 Follow-up period (Day 7 /+2 days)

Subjects will return to the study center on Day 7 for a Follow-up Visit. The following assessments will be performed (refer to the Time and events schedule [Table 5] for further details):

- Physical examination (including body weight)
- 12-lead ECG
- Vital signs (including supine blood pressure, pulse rate and infra-axillary body temperature)
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis; pregnancy test for female)
- eGFR
- AE and concomitant medication recording

Subjects who are withdrawn from the study should, where possible, complete the procedures scheduled for the Follow-up Visit as soon as possible after withdrawal.

5.2.4 Unscheduled visits

An unscheduled visit is defined as any visit to the study center outside of the Protocol specified time-points due to safety reasons or when a repeated measurement is required (e.g., obvious measurement errors, measuring device failure, confirmation of out-of-range results), where the subject is seen by study personnel.

6 STUDY PROCEDURES

Procedures will be performed according to the Time and events schedule (Table 5).

The time point for PK blood collection takes priority over any other scheduled study activities. Where other activities are scheduled together with PK blood collection, these will be performed before or after the blood collection and PK blood collection will be done exactly at the scheduled time point. ECG and vital signs (except body temperature) will be measured before blood collection for PK and safety assessments will be performed.

Time windows for relevant assessments will be described in a separate document.

6.1 Demography

Date of birth, sex, weight, height, race, smoking habits and alcohol consumption habits will be recorded in the CRFs.

6.2 Medical history and prior medication

Any significant and relevant past conditions and any current medical conditions prior to Screening will be recorded in the CRFs. At Screening, subjects will be asked what medications they have taken during the last 3 months. Medication taken within 30 days of Screening will be recorded as prior medication in the CRFs.

6.3 Concomitant medication

Concomitant medication is defined as any medication, other than the IMP, which is taken during the study, including prescription and over the counter medications. All concomitant medications used from the Screening visit to the last scheduled visit must be recorded in the CRFs with their daily dosage, route, duration, and reasons for administration.

6.3.1 Permitted medication

Medicines which, in the opinion of the Sponsor and Investigator, will not interfere with the study procedures or compromise safety may be used. On-demand use of acetylsalicylic acid for mild analgesia or use of oral contraceptives is permitted without discussion with the Sponsor.

In addition, any other concomitant medication may be given only if deemed necessary for the subject's welfare by the Investigator or the subject's personal physician. In subjects with hepatic insufficiency, the use of prescribed medications is permitted as described in Attachment 3. However, the subjects with normal hepatic function are restricted from use of any concomitant medications unless discussed and agreed with the Sponsor.

6.3.2 Prohibited medication

Subjects must not participate in any other clinical study involving administration of an IMP for the duration of the current study.

Subjects must not take any prescribed or non-prescribed systemic or topical medication (including herbal remedies) unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study procedures or compromise safety.

Albumin preparation must not be administrated within 14 days before the Screening and from 14 days before Day -1 (check-in) to Day 3 (discharge).

The following medications must not be administrated from Day -1 to Day 3 (treatment hospitalization period).

- Antibiotics (e.g., cefazolin sodium, cefotiam hydrochloride, piperacillin sodium, etc.*)
  *: except for kanamycin and rifaximin for use in treating hepatic encephalopathy by oral administration. Other antibiotics used in treating hepatic encephalopathy can be administrated when the Sponsor agrees.
- Strong sulfotransferase inducers or inhibitors (e.g., mefenamic acid, acetaminophen and ibuprofen)
- Strong UGT inducers or inhibitors (e.g., diclofenac sodium)

6.3.3 Rescue medication

There is no known antidote to MCI-186. Full resuscitation facilities will be available at all times.

6.4 Child-Pugh classification

Child-Pugh classification bases on two clinical features (encephalopathy and ascites) and three laboratory-based parameters (albumin, bilirubin, and prothrombin time). The Child-Pugh score is calculated by adding the scores of the five factors (Table 6).The degree of hepatic impairment is categorized into mild, moderate, and severe as summarized in Table 7. The subjects will be stratified to three different groups of hepatic function according to their total score of Child-Pugh (normal and mild or moderate impairment) at Day -1.

Table 6 Child-Pugh Points Scored for Observed Findings

	Points score for increasing abnormality		
Factor	**1 point**	**2 points**	**3 points**
Hepatic encephalopathy	none	I - II	III - IV
Albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
Ascites	absent	slight	moderate
Bilirubin (mg/dL)	<2	2 – 3	>3
Prothrombin time (sec prolonged)	<4	4 – 6	>6

Table 7 Assessment of Severity of Hepatic Impairment by Total Score

Total score	**Severity of hepatic impairment**
5 – 6	Mild (Grade A)
7 – 9	Moderate (Grade B)
10 – 15	Severe (Grade C)

An experienced physician of the study center will assess hepatic encephalopathy by performing a standard neurological examination, which includes handwriting and common amnestic testing.

Encephalopathy will be graded as follows:

Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade I: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
Grade II: lethargic, time-disoriented, inappropriate, asterixis, ataxia
Grade III: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity
Grade IV: unrousable coma, no personality/behaviour, decerebrate

6.5 Estimation of GFR (eGFR)

GFR will be estimated using the 3-variable Japanese equation.

equation of GFR for Japanese [7]:

$$eGFR\ (mL/min/1.73\ m^2) = 194 \times (S_{cr,\ std})^{-1.094} \times (Age)^{-0.287} \times (0.739 \text{ if female})$$

$S_{cr,\ std}$: serum creatinine measured with a standardized assay (mg/mL)

6.6 Pharmacokinetic assessments

6.6.1 Collection of blood samples for PK analysis

[redacted]

[redacted]

6.7 Safety assessments

Please refer to Section 8 for details of AE management.
The results of safety assessments will be recorded in the CRFs.

6.7.1 Physical examination

At the times indicated in the Time and events schedule (Table 5), subjects will undergo a routine assessment of major body systems (general appearance, cardiovascular, neurological, respiratory, head, eyes, ear/nose/throat, lymph nodes, abdominal, hepatic, gastrointestinal, musculoskeletal, neck, dermatological, and 'other').

Body weight will be measured at the times indicated in the Time and events schedule (Table 5). Height will be measured once only (at Screening). The BMI will be calculated using the standard formula at Screening.

Body mass index calculation:

$$BMI = Weight\ [kg] / (Height\ [m])^2$$

6.7.2 Vital signs

At the times indicated in the Time and Events Schedule (Table 5), subjects will undergo an assessment of systolic blood pressure (SBP) and diastolic blood pressure (DBP) using an automatic blood pressure measurement device with an appropriate cuff size after the subject has rested for at least 5 minutes in a supine position. 3 repeated measurements will be performed and a mean of the measurements will be calculated. The same arm will be used for all measurements. Pulse rate (beat/min) and infra-axillary body temperature will also be measured.

The Investigator will perform an overall evaluation for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

6.7.3 Electrocardiogram

At the times indicated in the Time and Events Schedule (Table 5), a 12-lead ECG will be performed after the subject has rested for at least 5 minutes in the supine position.
The following ECG parameters will be recorded: heart rate, RR-interval, PR-interval, QRS duration, QT-interval and QTc. The QTc-interval will be calculated automatically according to Fridericia's formula. In case of results >450 ms in healthy subjects or hepatic impairment subjects, repeat measurements will be performed.
The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal

not clinically significant (NCS)'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

6.7.4 Routine laboratory evaluations

Blood and urine samples will be collected for routine clinical laboratory safety evaluations according to Table 5. The laboratory safety evaluations performed during the study are presented in Table 8.

Additional laboratory safety evaluations will be performed at other times, if judged to be clinically appropriate, or if the ongoing review of the data suggests a more detailed assessment of laboratory safety evaluations is required.

The Investigator will perform a clinical assessment of all laboratory safety data and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

Table 8 Routine laboratory evaluations

Haematology:	
Haemoglobin	Mean corpuscular haemoglobin (MCH)
Haematocrit	Mean corpuscular haemoglobin concentration (MCHC)
Platelet count	Mean corpuscular volume (MCV)
Red blood cell (RBC) count	White blood cell (WBC) count and differential
Biochemistry:	
Alkaline phosphatase (ALP)	Uric acid
Aspartate aminotransferase (AST)	Protein (total)
Alanine aminotransferase (ALT)	Albumin
Gamma-glutamyl transpeptidase (GGT)	Cholesterol
Potassium	Triglycerides
Sodium	High density lipoprotein-cholesterol (HDL-C)
Chloride	Low density lipoprotein-cholesterol (LDL-C)
Calcium	Lactate dehydrogenase (LDH)
Inorganic phosphate	Amylase
Glucose	Creatine kinase (CK)
Blood urea nitrogen	Creatinine[1, 2]
Bilirubin (direct and total)	Follicle stimulating hormone (FSH)[3]
Coagulation:	
Prothrombin time	Activated partial thromboplastin time (aPTT)
Urinalysis:	
Specific gravity, sediment, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood	
hCG[4]	
Microscopic examination[5]	
Serology:	
Hepatitis B surface antigen (HBsAg)	Human immunodeficiency virus (HIV) antigen/antibodies
Hepatitis C virus antibody (HCVAb)	
Drugs and alcohol screen:	
Phencyclidine, cocaine, barbiturates, tetrahydrocannabinol, benzodiazepines, amphetamines/methamphetamines, opiates, and alcohol breath test	

[1] eGFR will be calculated using the 3-variable Japanese equation
[2] eCLcr will be calculated using the Cockcroft-Gault formula
[3] Females only; performed at Screening only
[4] Females only; a urine pregnancy test will be performed at Screening, Day -1 and follow-up
[5] Performed only if required, based on urinalysis results

Blood and urine samples will be analysed by [redacted] using standard methods. Laboratory safety measurements will be performed according to [redacted] SOPs. Procedures for the handling of samples will be described in full in a separate document.

6.8 Total blood volume

The approximate total blood volume taken per subject is given in Table 9.

Table 9 Blood volumes

Type of sample	Sample volume (mL)	No. of Samples	Total volume (mL)
Haematology	2	5	10
Biochemistry	8	5	40
Coagulation	1.8	5	9
Serology	8	1	8
[redacted]			
		Overall total	[redacted]

Additional or repeat safety laboratory samples may be taken during the study if required by the Investigator. The volume to be drawn from each subject will be approximately [redacted]

7 STUDY TREATMENT

7.1 Investigational Medicinal Product

A description of the IMP is given in Table 10.

Table 10 Investigational Medicinal Product

	MCI-186 injection
Dosage form	Aqueous solution for injection
Description	Clear and colorless
Strength	30 mg of edaravone per 20 mL ampule
In active excipients (per 20 mL ampule)	Sodium bisulfite: 20 mg L-cysteine hydrochloride hydrate 10 mg Sodium chloride: 135 mg Sodium hydroxide: q.s. Phosphoric acid: q.s.
Storage conditions	Room temperature

IMP (MCI-186 injection) will be manufactured by the Sponsor. Commercially available drug product, RADICUT® inj. 30mg manufactured by [redacted], is overlabelled.

Ten overlabelled ampules will be packed in a paper carton and certified by the Sponsor.

IMP is tested and released according to Good Manufacturing Practice.

IMP will be labeled with the Sponsor's name and address, chemical name or identification code, and storage conditions. The label will contain the statement: "Investigational Product: to be used in a clinical investigation only" or other similar statement. All labelling will comply with applicable regulatory requirements.

7.1.1 Compliance

IMP will be administered by the Investigator or designee. The prescribed dosage, timing and mode of administration of study medication may not be changed. Any departures from the intended regimen must be recorded in the CRF.

IMP accountability and subject compliance will be documented throughout the study period using study-specific IMP dispensing. The Investigator, or suitably qualified staff member, will supervise/oversee the administration of IMP and the exact time of dosing will be recorded in the CRF.

7.1.2 Shipping, receipt, handling and storage

IMP will be shipped from [redacted] to the clinic in a temperature-controlled shipping system after completion of a clinical contract between the Sponsor and study center.

On receiving a shipment of the IMP at the study center, the designee will conduct an inventory check and complete a supplies receipt document, and the receipt will be returned to the Sponsor. The designee will maintain a record of all IMPs received and returned.

At the study center, IMP will be stored at room temperature in a locked, restricted access area. The temperature will be recorded throughout the study and a daily minimum and maximum temperature log will be maintained. A temperature log recording will be

maintained daily throughout the course of the study. Any temperature deviations will be reported to the Sponsor.

7.1.3 Dispensing

The treatments will be dispensed by the Investigator or designee. A record of the IMP dispensed to each subject will be maintained by the designee in an Accountability Log. Any opened ampule will not be redispensed.

Investigator or designee will dilute one ampule (30 mg of MCI-186) with 100 mL of physiological saline. All subjects will be administered intravenous infusion 30 mg of MCI-186 over 60 minutes in the morning of Day 1 by the Investigator or designee.
Detailed procedure is described in a separate document.

7.1.4 Accountability, returns and destruction

During the study, the designee will record the receipt, dispensing, return, non-use or other disposition of IMP including the date, quantity, batch or code number, and identification of subjects (subject number) who receive the IMP in an Accountability Log. IMP accountability (drug reconciliation) will be checked by the Sponsor. IMP is to be used only for this Protocol and not for any other purpose.

All unused IMP must be stored at the study center until it to be returned to the Sponsor.

7.2 Subject identification

At Screening, each subject will be assigned a unique Subject Number by which the subject will be subsequently identified. Subjects dropping-out or withdrawing, for any reason, without completing all screening evaluations successfully, will be considered as `screen failures'. The Investigator will keep a screening log of all subjects screened in order to assess the numbers and characteristics of the excluded subjects, and the reasons for their exclusion. The Subject Number will be documented and kept in the study center. The Subject Number will be used to identify subjects on IMP labels and other documentation.

The investigator will provide a subject screening list and a registration list of the hospitalization to the sponsor when requested. In the provision, adequate attention should be paid to the privacy of patients and protection of personal information.

Subjects who are withdrawn for non-treatment related reasons may be replaced at the discretion of the Sponsor and Investigator. Especially, in the normal hepatic control group (Group 3), a few substitute subjects will enter the study center at Day -1 and remain on-site until Day 1. The substitute subject will receive the same treatment assigned to the subject he/she replaces. Subjects withdrawn as a result of treatment-related AEs thought to be causally related to the study medication will generally not be replaced.

7.3 Procedures for assigning subjects to treatment groups

The subjects will be stratified to three different groups of hepatic function according to Child-Pugh classification (normal and mild or moderate impairment) at Day -1. The Subject Group will be recorded in the CRFs.

8 ADVERSE EVENT MANAGEMENT

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs that occur from the time written informed consent is obtained until the end of the Safety Follow-up Period will be recorded in the CRF. Even if the AE is assessed by the Investigator as not related to IMP, its occurrence must be recorded in the source documents and CRF. AEs will be classified as 'baseline' if they occur before the administration of IMP. AEs will be classified as 'treatment-emergent' if they arise following the first administration of IMP or if a pre-dose AE increases in severity following dosing.

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. The questioning should be open-ended and non-leading.

8.1 Definition of an adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

8.2 Definition of a serious adverse event

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

- Results in death.
- Is life-threatening.
- Requires hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Any event that is as serious as the above cases.
- Is a congenital anomaly or birth defect.

Medical and scientific judgement should be exercised in deciding whether an AE is serious and whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room, at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse. These should also usually be considered serious.

The term 'life threatening' refers to an event/reaction in which the subject 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.

Admission to a hospital as a new inpatient is deemed as meeting this criterion, even when the length of hospital stay was less than 24 hours. Transfer to other departments of the same hospital due to a newly emerged event during the hospitalisation (e.g., transfer from the psychiatry ward to the internal medicine ward, from the internal medicine ward to the coronary intensive care unit, or from the neurology ward to the tuberculosis ward) is also counted as hospitalisation.

SAEs will be recorded and reported as described in Section 8.7.

8.3 Severity of adverse events

The severity of AEs will be classified according to the following criteria:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes discomfort and interferes with the subject's general condition.

Severe: The event causes considerable interference with the subject's general condition and may be incapacitating.

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:

The term 'severe' is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as 'serious', which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.4 Relationship of adverse events to Investigational Medicinal Product

The causal relationship of the AE to IMP will be determined as either 'reasonable possibility' or 'no reasonable possibility' defined as:

Reasonable Possibility – The relationship of the clinical event to the IMP makes a causal relationship possible, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

No Reasonable Possibility – The relationship of the clinical event to the IMP makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

8.5 Clinical laboratory abnormalities and other abnormal assessments

Laboratory abnormalities which are clinically significant will be recorded as AEs or SAEs. The Investigator will exercise medical judgment in deciding whether abnormal laboratory values are clinically significant.

It should be noted that for subjects with hepatic disease the biochemistry and haematology parameters may be outside of the normal reference range for healthy volunteers as a function of the underlying disease. Therefore, the change from baseline of the laboratory parameter is an important indication in the subjects with hepatic impairment.

If an abnormal laboratory value or assessment is clearly related to a medically-defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE form, not the individual laboratory values.

All clinically significant abnormal laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or stabilise, or until they are judged by the Investigator to be no longer clinically significant.

8.6 Recording and reporting of adverse events

All AEs, regardless of the relationship to IMP, occurring from the time written informed consent is obtained from a subject until the end of the safety Follow-up Period or the withdrawal of the subject from the study will be recorded.

All AEs will be recorded on an AE form in the CRF. Reports should contain a description of the event, date and time of onset, date and time of resolution, severity, treatment required, relationship to IMP, action taken with the IMP, outcome and whether the event is classified as serious.

The Investigator will evaluate the severity of the AEs (as defined in Section 8.3) and will assess the causality between the AEs and the IMP (as defined in Section 8.4).

Pre-existing illnesses, which started prior to entry and is still ongoing at the start of the study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as medical history.

If the Investigator becomes aware of any new safety information, or any safety information which appears to be either study or IMP related after the final Follow-up Period, then they must notify the Sponsor immediately.

8.7 Recording and reporting of serious adverse events

All SAEs occurring from the time written informed consent is obtained from a subject until the end of the safety Follow-up Period or the withdrawal of the subject from the study must be notified to the Sponsor via fax on the SAE Uniform Form within 24 hours of the Investigator becoming aware of the SAE.

The SAE report should be completed as thoroughly as possible, including an assessment of causality. All such reports will identify subjects by unique code numbers assigned to the study participants, rather than by the subjects' names, personal identification numbers, or addresses. The SAE report should be signed and dated by the Investigator.

The reporting contact for SAEs via fax is as follows:

Fax Number: [redacted]

Reports of pregnancy, although not classified as an SAE, will be handled and reported as in Section 8.8.

The Sponsor will comply with the applicable regulatory requirements related to the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the Regulatory Authorities, the other Investigators and the Head of the study center. The Investigator will be responsible for informing the Head of the study center of SAE or SUSARs, as per local laws and requirements.

8.8 Pregnancy

If a female subject who has been exposed to the IMP becomes pregnant, the course and outcome of the pregnancy should be monitored and documented. Where possible, if a female partner of a male subject who has been exposed to the IMP becomes pregnant and the subject provides this information, then the pregnancy will be documented based on information provided by the subject.

Pregnancy occurring in a female subject who has been exposed to the IMP, although not classified as an SAE, must be reported using the same timelines and contact details as an SAE (Section 8.7) but *via* a paper Mitsubishi Tanabe Pharma Pregnancy Notification Form (Attachment 4). If the outcome or course of the pregnancy involves an SAE (e.g., a congenital anomaly), then an SAE form *via* fax/e-mail needs to be completed in addition to the updated paper Mitsubishi Tanabe Pharma Pregnancy Notification Form. Termination of pregnancy for medical reasons, spontaneous abortion and congenital birth defects should always be reported as SAEs.

8.9 Follow up of adverse events

The Investigator should follow up subjects with AEs/SAEs, until the event has resolved or stabilized and any abnormal laboratory values have returned to baseline; or until there is a satisfactory explanation for the changes observed. If there are unresolved AEs at the Follow-up visit (Day 7/+2 days), the Investigator should follow up at least 21 days after Follow-up visit. In the case of death, if possible a pathologist's full report should be supplied.

8.10 Reference safety information

The reference safety information for this clinical study is the Investigator's Brochure.

8.11 Overdose

Any subject who takes an overdose should be given the standard medical care.

If the subject takes a dose which is greater or more frequent than that specified in the Protocol (with or without associated symptoms), this must be reported to the Sponsor immediately or within 24 h of awareness via a SAE form (using the contact details in Section 8.7).

If the subject experiences any associated symptoms as a result of the overdose, the Investigator will record this as a separate (S)AE.

9 DATA COLLECTION AND PROCESSING

9.1 Data collection

Subject data will be collected on individual paper CRFs and will be substantiated by source documents (such as laboratory reports, medical records or ECGs) at the study center. All relevant data will be transcribed into the CRF from source documents, entered into the study database directly from source documents, or transferred electronically to the study database. Where no printed or electronic source documents exist, data will be entered directly into the CRF and the CRF will be considered the source document. Inclusion or exclusion criteria, results of physical examinations, adverse events, subject disposition and comments of investigator on any issues in the CRF may be considered the source document. The specified contents as the source document in the CRF will be documented separately from the Protocol by the Investigator and Sponsor.

Prior to the start of the study, the Investigator will complete a Staff Signature Log and Site Delegation Tasks. The Sponsor will provide training for completion of the CRF. The CRF will be completed according to guidelines provided by the Sponsor in writing, and verbally.

Completed CRFs will be reviewed by the Study Monitor for the study to ensure data accuracy, completeness and consistency. Any discrepancies found during the CRF review or during data validation and/or quality assurance reviews of the data by data management or other functions are to be clarified by the Investigator on paper Data Clarification Form (DCF).

The Investigator or designee must record all required subject data using the previously specified data collection method defined by the Sponsor. An explanation must be documented for any missing data. The Investigator must seal with print name or sign and date a declaration on the CRF attesting to his/her responsibility for the quality of all data recorded, and that the data represents a complete and accurate record of each subject's participation in the study. The original completed CRF will be returned to the Sponsor, and a paper copy will be retained by the Investigator.

9.2 Case Report Form completion

The CRF will be presented in a booklet. The Subject Number should always be indicated and date (and time, if applicable) of each assessment should be entered in the CRF.

CRFs must be completed in timely manner so that this does not delay the ongoing data validation, review and quality control. Each paper CRF must be filled in neatly with a black- or blue-inked ballpoint pen. The final, completed CRF for each subject must be sealed with print name or signed and dated by the Investigator on the appropriate CRF page to signify that he/she has reviewed the booklet and certifies it to be complete and accurate.

Errors must be corrected by drawing lines through the incorrect entry and by writing the new entry as close to the original as possible. The original entry must not be completely obscured. The correction must then be sealed with print name or signed and dated by an authorized individual (who must be included on the Staff Signature Log and Site Delegation Tasks). The use of erasers or correction pen, tape or fluid is not allowed. Errors found after providing to the Sponsor should be clarified by the Investigator on the DCF.

9.3 Data processing

The data collected on the CRFs will be captured in a specially constructed and validated database. The data will be validated using both manual and electronic means. Clarification of data will be requested from the study center as required. An audit trail of the original database entries, changes and deletions, session dates and times and the credentials of the database user who performed the operation will be maintained by the system. The completed database will be quality assured and locked to prevent further changes. A full database extract will be made available for statistical analysis according to the methods outlined in Section 10 and the Statistical Analysis Plan (SAP).

AEs and medical history entries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the WHO Drug Dictionary. Versions of the dictionaries used will be documented in the Data Management Plan and SAP.

10 STATISTICAL METHODS AND PLANNED ANALYSES

10.1 Determination of sample size

The planned sample size of six evaluable subjects per hepatic impairment subjects group and per healthy subjects group is not based on a power calculation, but is according to FDA guidance for hepatic impairment PK study.
Eight subjects per group will be included to obtain at least six evaluable subjects.
In total, 24 subjects will be included to obtain 18 evaluable subjects.

10.2 Analysis sets

The statistical analysis will be based on separate analysis sets, defined as follows:

Safety analysis set:	All subjects who have received at least one dose of IMP.
PK analysis set:	All subjects, who have received at least one dose of IMP and for whom the PK data are considered to be sufficient and interpretable.

10.3 Statistical analysis

10.3.1 General considerations

A SAP containing detailed data handling, analysis methods, outputs (tables, figures and listings) will be developed and approved prior to database lock. Additional analysis may be performed if deemed necessary. Any deviations from the planned analysis will be described and justified in a separate document and in the CSR.

All variables will be summarized by each group (Group 1, 2 and 3). Unless otherwise stated, continuous data will be summarized descriptively using N (number of subjects), n (number of observations), mean, standard deviation, minimum, median and maximum. Categorical data will be summarized using frequency tables (frequency and percentage).

All individual subject data will be listed.

10.3.2 Data handling

Procedures for the handling of any missing, unused or spurious data will be described in the SAP.

10.3.3 Analysis of demography and other baseline subject characteristics

Demographic and other baseline variables include age, sex, height, weight, race, medical history and concomitant medication.

Age, sex, height, weight, race, medical history and prior and concomitant medication will be summarized by each group and listed by subjects. Age will be calculated as the integer difference in years from date of birth to informed consent date.

10.3.4 Analysis of primary endpoints

The following primary PK parameters of MCI-186 will be calculated in the study:

- Peak drug concentration (C_{max});
- Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$);
- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}\infty}$);

The parameters will be determined from individual concentration-time data of MCI-186 in plasma by non-compartmental analysis methods using [redacted] The actual, exact sampling times in relation to dosing will be used. For calculation of PK parameters, concentrations below the limit of quantification (BLQ) will be imputed with a value of zero.

C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}\infty}$ of MCI-186 will be summarized per group (by hepatic function) with mean, median, geometric mean, minimum value, maximum value, standard deviation, and coefficient of variation (%).

The primary PK endpoints will be presented and summarized along with the secondary PK endpoints, as described in Section 10.3.5.1.

Additional analyses may be described in a SAP and performed when necessary.

10.3.5 Analysis of secondary endpoints

10.3.5.1 Pharmacokinetic endpoints

In addition to the primary PK endpoints the following PK parameters will be determined, where possible, from the individual concentration-time data of MCI-186 and its metabolite in plasma by non-compartmental analysis methods using [redacted] The actual, exact sampling times in relation to dosing will be used. For calculation of PK parameters, concentrations below the limit of quantification (BLQ) will be imputed with a value of zero.

<u>PK parameters of MCI-186</u>

- Half-life ($t_{½}$);

[redacted]

Individual and mean plasma concentration versus time curves will be plotted by each group (Group 1, 2 and 3) on both linear/linear and log/linear scales separately for MCI-186 and its metabolite.

Individual plasma concentration of MCI-186 and its metabolite will be listed.

Summary statistics (number of subjects [N], n, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) will be calculated for plasma concentrations of MCI-186 and its metabolite at each group (Group 1, 2 and 3). For the calculation of the summary statistics, concentration values reported as BLQ will be set to zero.

The PK parameters will be summarized. Summary statistics (N, n, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) will be presented for all PK parameters by each group (Group 1, 2 and 3).

The following graphics will be produced for the relationship between measures of hepatic function (on the horizontal axis) and $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, [redacted] and C_{max} of MCI-186 (on the verticalaxis):

For each hepatic function group: Scatter plots of $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, [redacted] and C_{max} of MCI-186 versus Child-Pugh score, albumin, bilirubin, prothrombin time and eGFR with regression line.

The statistical analysis will be to estimate the ratio of mean pharmacokinetic parameters of each hepatic function group (Groups 1 or 2) with respect to the normal hepatic function group (Group 3). The $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and C_{max} of MCI-186 for the statistical analysis will be the log-transformed estimated AUCs and C_{max}. Only the data from subjects who completed the study will be included in the statistical analysis. If 1 pharmacokinetic parameter of interest is not estimable for a given subject, the subject's data will not be included in the statistical analysis of that particular pharmacokinetic parameter. An analysis of variance (ANOVA) model that includes hepatic function as fixed effects, will be used to estimate the least squares means and intersubject variance.

Using these estimated least squares means and intersubject variance, the point estimate and 90% confidence intervals for the difference in means on a log scale between each impaired hepatic function group and the normal hepatic function group will be constructed. The limits of the confidence intervals will be retransformed using antilogarithms to obtain 90% confidence intervals for the ratios of the mean $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and C_{max} of MCI-186 between each impaired hepatic function group and the normal hepatic function group.

10.3.5.2 Safety endpoints

The objective of the evaluation is to investigate safety and tolerability of MCI-186. All safety and tolerability variables will be listed and summarized descriptively. There will be no formal statistical analysis of the safety data. In general, safety data will be summarized separately by each group (Group 1, 2 and 3) and/or day, as appropriate.

10.3.5.3 Adverse events

Adverse events will be coded using MedDRA (version 18.1 or later). A by-subject AE data listing including start/stop times, verbatim term, Preferred Term, System Organ Class (SOC), dose level, severity, seriousness, relationship to treatment and outcome will be provided. All AEs that start before dosing will be classified as baseline AEs and will be listed only. All treatment-emergent AEs (TEAEs), i.e., AEs which start on or after dosing,

will be tabulated. In the tabulations, numbers of subjects with TEAEs and numbers (occurrences) of TEAEs will be counted separately.

The following summaries of TEAEs will be presented:

- Summary of AEs by SOC and Preferred Term
- Summary of AEs by SOC, Preferred Term and severity of event
- Summary of AEs by SOC, Preferred Term and relationship to treatment

The above TEAEs summaries will be produced by time interval as appropriate.

In addition, details of AEs and SAEs leading to withdrawals will be listed separately.

10.3.5.4 Vital signs and electrocardiograms

Vital signs and 12-lead ECG variables and changes from baseline will be summarized (N, n, mean, SD, median, minimum and maximum) at each time point by each group (Group 1, 2 and 3).

The baseline for the vital sign parameters and 12-lead ECG measurements will be the last valid assessment obtained on Day 1 prior to the administration of IMP (Day 1, pre-dose).

10.3.5.5 Routine safety laboratory tests

Laboratory variables and changes in laboratory variables from baseline will be summarized (N, n, mean, SD, median, minimum and maximum) at each time point for each group (Group 1, 2 and 3). Baseline will be Day -1.

Urinalysis variables will be listed by subject and time point.

Values outside the normal ranges (provided with the laboratory report), will be flagged in the subject data listings.

10.3.5.6 Prior and concomitant medication

Prior and concomitant medication will be coded according to the WHO DD using the current version and Anatomical Therapeutic Chemical (ATC) classification system. These categories will be tabulated and summarized by each group (Group 1, 2 and 3). Incidence tables will be summarized with ATC level 2 code and text (e.g. 'N02 – Analgesics') and preferred name for each group (Group 1, 2 and 3). Prior and concomitant medications will be listed by subject including the full ATC code, text, and Preferred Term.
Prior or concomitant medication data will be summarized by each group.

10.3.5.7 Physical examination

Physical examination data will be listed by subject. Changes in physical examinations will be described in the text of the CSR.

10.3.6 Analysis of exploratory endpoint(s)

Not applicable in the study.

10.3.7 Interim analysis

Not applicable in the study.

11 STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS

11.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in compliance with the 2013 (Fortaleza, Brazil) revision of the 1964 Declaration of Helsinki. This study will also be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and Japan-GCP. This study will also be carried out in accordance with regional and local legal requirements. Before the first subject is enrolled in the study, all ethical and legal requirements will be met.

11.2 Investigator responsibilities

11.2.1 Informed consent

The investigator will prepare an ICF. The ICF will be submitted to the Sponsor, and approved by the IRB prior to the start of the study.

Prior to undergoing any study-specific procedure, all legally competent subjects must consent in writing to participate. An ICF will be given to each subject, which will contain all regulatory-required elements, all ICH-required elements, and data protection information, when applicable, in language that is understandable to the subject.

The process of obtaining the informed consent will be in compliance with all regulatory regulations, ICH requirements, and local laws.

Either the Investigator or a designated person, qualified to meet any applicable local regulations, who is equally knowledgeable about the study will explain the aims, methods, anticipated benefits and potential hazards of the study and any discomfort it may entail. The review must be in a form understandable to the subject. A corresponding written explanation will also be provided and the subject allowed sufficient time to consider the study information.

If the subject is willing to participate in the study, the ICF will be sealed with printed name or signed and dated by the subject, the Investigator and, if applicable, the designated person who explained the nature of the study. The subject will receive a copy (together with the information sheet) and the original ICF will be retained with the study records at the study center.

The date (and time, if required) on which the ICF is signed by the subject must be recorded in the source notes.

The Investigator or his/her designee must emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB. The study center personnel must use the amended ICF for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects.

11.2.2 Contact to other attending physicians

The investigator (or subinvestigator) will confirm during the Screening period whether subjects have medical attention by other doctors. When subjects are visiting his/her doctors, the investigator (or subinvestigator) will inform his/her doctors of the participation in the study upon his/her consent. In addition, the investigator, subinvestigator or the investigational staff will issue a study participation card to the subjects and instruct them to present the card to doctors when subjects visit other hospitals.

11.2.3 Ethical and regulatory approval

The study must be conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, ICH-GCP, Japan-GCP and the Protocol. The Investigator and Sponsor will sign this Protocol to confirm agreement to abide by it.

Before any study-related procedure is performed on a subject, IRB, regulatory and local approvals of this Protocol will be obtained. While the study is ongoing and at study completion/discontinuation, the Sponsor or Investigator will submit information to the IRB(s) in accordance with institutional/local regulations, for example:

- Information on SUSARs
- Periodic reports on the progress of the study
- Notification of the end of study or early termination
- Final study summary upon completion or closure

The Sponsor will ensure that any SUSARs from this study and other studies with this IMP are reported promptly to the regulatory authorities.

If it is necessary to amend the Protocol during the study, proper notification will be made to the IRBs or Regulatory Authority depending on the nature of the modification. Protocol Modification requiring IRB approval may be implemented only after a copy of the IRB's approval/favourable opinion letter has been transmitted to the Sponsor. Protocol Modification that is intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor and IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

Any Protocol or other deviations that occur during the study will be documented and reported to the Sponsor by the Investigator. Depending on the nature of the deviation, this may be reported to the appropriate Regulatory Authority, the Head of the study center and the IRB.

The Investigator and the Sponsor should sign the Protocol to confirm agreement.
Before implementing the study, the Protocol and any other appropriate documents must be reviewed and approved by the IRB and the appropriate Regulatory Authority.

The Head of study center will forward to the Sponsor or Investigator a copy of the written approval of the IRB and any other approving bodies.

11.2.4 Source document requirements and document access during the study

The Investigator or a designated person by the Head of study center must retain a comprehensive and centralized filing system of all study-related documentation (including, but not limited to: essential documents, copies of Protocols, CRFs, source data such as original reports of test results, IMP dispensing logs, correspondence, records of informed

consent, and other documents pertaining to the conduct of the study) that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator/institution will permit study-related monitoring, audits, IRB reviews and regulatory inspections providing direct access to source data/documents.

11.2.5 Study records retention

Study-related documentation must be kept for at least 3 years or until notified by the Sponsor. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

11.3 Study monitoring

In accordance with applicable regulations, GCP, and the procedures of the Sponsor or its designees, the Study Monitor will periodically contact the study center, and conduct on-site visits. The extent, nature, and frequency of on-site visits will be based on study complexity, enrolment rate, and data quality at the study center. Through these visits and frequent communications (e.g., letter, email, and telephone), the Study Monitor will verify that the investigation is conducted according to Protocol, regulatory and Sponsor requirements.

The Investigator and Head of study center will allow the Study Monitor direct access to all relevant documents, and allocate his/her time and the time of his/her personnel to the Study Monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the Study Monitor will contact the study center personnel prior to the start of the study to discuss the Protocol and data collection procedures.

At study closure, the Study Monitor will conduct all activities as indicated in Section 11.5.

11.4 Quality assurance and auditing

Authorized representatives of the Sponsor, IRB and/or regulatory authorities may conduct an audit or inspection of this study either during or after completion. In such cases, the Investigator will give the auditor/inspector direct access to all relevant documents and source data, and will allocate his/her time and the time of his/her personnel as may be required to discuss findings and any relevant issues.

11.5 End of study and site closure

The end of the study is defined as the last visit for the last subject. Upon completion of the study, or if the study or an Study center is prematurely discontinued, the following activities, where applicable, must be conducted by the Study Monitor in conjunction with the Investigator:

- Return of all study data to the Sponsor
- Completion of data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused IMP
- Review of the study center study records for completeness

11.6 Premature discontinuation of the study

The Sponsor reserves the right to discontinue the study because of safety concerns, ethical issues or serious and/or persistent non-compliance with the Protocol.

Stopping the study or amendment the regimen criteria are described in Section 4.5.

If, in the opinion of the Investigator, the clinical observations in this study suggest that it may be unwise to continue, the Investigator may terminate part of, or the entire study, after consultation with the Sponsor. In addition, the Sponsor may terminate part of, or the entire study, for safety or administrative reasons. If the study is suspended or terminated, the Sponsor will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator is responsible for promptly informing the IRB, and providing the reason(s) for the suspension or termination of the study.

For all subjects, the Follow-up Visit assessments should be performed, as far as possible (Section 5.2.3).

Any unresolved AE or SAE will be followed up according to Section 8.9.

In the event that a subject elects not to return to the study center for the end of study visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the CRF. The study center personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required end of study assessments.

In addition, all general study center activities required for the scheduled end of study and site closure should be completed, as described in Section 11.5.

11.7 Premature discontinuation of individual Investigator sites

The Sponsor may at any time, at its sole discretion, discontinue the study center for various reasons, including, without limitation, the following:

- Failure of the Investigator to enrol subjects into the study at a reasonable rate
- Failure of the Investigator to comply with applicable laws and/or pertinent regulations
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or regulatory authorities
- Insufficient adherence to Protocol requirements

The Sponsor will issue a written notice to the Investigator, which will contain the reasons for taking such action. If the study center is terminated for non-compliance, appropriate regulatory authorities will also be notified by the Sponsor.

For all subjects, the Follow-up Visit assessments should be performed, as far as possible (Section 5.2.3).

Any unresolved AE or SAE will be followed up according to Section 8.9.

In the event that a subject elects not to return to the clinic for the end of study visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the CRF. The study center personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required end of study assessments.

In addition, all general study center activities required for the scheduled end of study and site closure should be completed, as described in Section 11.5.

11.8 Liability and insurance

If study-related health damage occurs in subjects, except there is no causal relationship between the health damage and the study, the Sponsor will provide appropriate compensation based on the compensation standard by the Sponsor (contents of the compensation are defined as medical cost, medical allowance, and indemnity). In such cases, the Sponsor will not impose any burdens, such as proof of the causal relationship, to the subjects.

In order to ensure the implementation of compensation responsibility and liability for study-related injury to the subjects, the Sponsor will take appropriate actions including taking out an insurance.

12 DISCLOSURE OF DATA

12.1 Confidentiality

A Subject Screening and Enrolment Log will be completed at each study center for all subjects who signed an ICF. A Subject Identification Log, documenting the subjects' names, will be completed and retained at each study center for all subjects enrolled in the study.

Subject names will remain confidential and will not be included in the database supplied to the Sponsor or its designee. If the subject name appears on any document collected, e.g., hospital discharge summary, the name must be obliterated before the document is transmitted to the Sponsor or its designee. All study findings will be stored in electronic databases. The subjects will give explicit permission for representatives of the Sponsor, regulatory authorities, and the IRB to inspect their medical records to verify the information collected. Subjects will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with laws and regulations. All personnel involved in the study will observe and work within the confines of local data protection regulations.

All information concerning the product as well as any information such as clinical indications for the IMP, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor or designee, and are unpublished, are confidential and must remain the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained. The Sponsor has full ownership of the CRFs completed as part of the study.

12.2 Publication

By signing the study Protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the regulatory authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The Sponsor or designee will prepare a final report on the study.

The sponsor has the ownership of the information in the Protocol, and the information will be provided to the study personnel, such as the investigator, subinvestigator, or IRB, but the information must not be disclosed to any third party without agreement by the sponsor in writing, except when needed for the conduct of the study.

The study personnel at the study centers such as the investigator or sub-investigator must obtain an approval from the Sponsor beforehand when they publish the results or information of this study.

The sponsor can freely use the information obtained from this study for the purpose of reporting to regulatory authorities, and proper use and marketing of drugs.

13 IMPLEMENTATION STRUCTURE

13.1 Sponsor

Sponsor's implementation structure is listed in Attachment 5 and especially monitors are listed in Attachment 1.

13.2 Study centers and Investigators

Study centers and investigators are listed in Attachment 2.

14 REFERENCES

1. Investigator's Brochure of MCI-186 (ver. 20)
2. Mitsubishi Tanabe Pharma Corporation; Study report; Population pharmacokinetic analysis of MCI-186 in Japanese and Caucasians. Project No. 002525.
3. FDA Guidance for Industry– Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling. May 2003
4. EMA – Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. 17 Feb 2005
5. Hishida A. Determinants for the prognosis of acute renal disorders that developed during or after treatment with edaravone. Clin Exp Nephrol. 2009; 13:118–122
6. Hirano M. Clinical evaluation of liver injury in patients with acute ischemic brain stroke treated with edaravone. Hepatology Research. 2011; 41: 142–150
7. Imai E, Yasuda Y, Makino H. Japan association of chronic kidney disease initiatives (J-CKDI). JMAJ. 2011; 54: 403-405.

Contact information

Mitsubishi Tanabe Pharma Corporation

17-10 Nihonbashi-Koamicho, Chuo-ku, Tokyo 103-8405, JAPAN

Phone: [redacted] Fax: [redacted]

Contact for nights and holidays

On the holiday of the sponsor such as night (17:30 to next morning 9:00), Saturdays, Sundays, and national holidays, and year-end and new year, the below Emergency Contact Center will receive an emergency contact and relay the message to the monitor.

Emergency Contact Center, Mitsubishi Tanabe Pharma Corporation

[redacted]

[redacted]