Mitsubishi Tanabe Pharma Europe Ltd.

STUDY PROTOCOL

Protocol Number: MCI-186-E05

An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Severe Hepatic Impairment Compared to Subjects with Normal Hepatic Function

EudraCT Number:	2018-001163-23
IND Number:	126396
Investigational Medicinal Product:	MCI-186 (edaravone): Solution for Infusion, 30 mg/100 mL
Development Phase:	Phase I
Sponsor:	Mitsubishi Tanabe Pharma Corporation (MTPC) 17-10, Nihonbashi-Koamicho, Chuo-ku, Tokyo, 103-8405, Japan
Sponsor's EU Representative:	Mitsubishi Tanabe Pharma GmbH Willstätter Str. 30, 40549 Düsseldorf, Germany
Sponsor's Responsible Signatory:	[redacted]
Coordinating Investigator:	[redacted]
Protocol Version and Date:	Final v3.0 – 06 February2019 Incorporating Substantial Protocol Modification 2

TABLE OF CONTENTS

In-text Tables

CONTACT LIST

Sponsor Mitsubishi Tanabe Pharma Corporation (MTPC) 17-10, Nihonbashi-Koamicho, Chuo-ku, Tokyo, 103-8405, Japan	
Sponsor's EU Representative Mitsubishi Tanabe Pharma GmbH Willstätter Str. 30, 40549 Düsseldorf, Germany	
[redacted] Head of Clinical Development	Sponsor's Responsible Signatory
[redacted] Senior Medical Science Physician, Clinical Department	Sponsor's Responsible Physician
[redacted] Senior Statistician	Statistician

Clinical Research Organisation
[redacted]

Coordinating Investigator
[redacted]

Bioanalytical Laboratory
[redacted]

Protein Binding Laboratory
[redacted]

Study Monitoring
[redacted]

SIGNATURE PAGE (SPONSOR'S RESPONSIBLE SIGNATORY)

Protocol Number: MCI-186-E05

An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Severe 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 and the Declaration of Helsinki (Fortaleza, Brazil, 2013). It has undergone both medical and scientific review by competent Sponsor personnel.

Sponsor Signatory:
Signed on behalf of Mitsubishi Tanabe Pharma Corporation (MTPC)

[redacted] _____ [redacted]

Date

Head of ~~Clinical~~ Development
Mitsubishi Tanabe Pharma Europe Ltd. (MTPE)
Dashwood House, 69 Old Broad Street, London,
EC2M 1QS, United Kingdom

SIGNATURE PAGE (STATISTICIAN)

Protocol Number: MCI-186-E05

An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Severe 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 and has undergone statistical review.

Statistician:
Signed on behalf of Mitsubishi Tanabe Pharma Corporation (MTPC)

[redacted]

[redacted]
Date

SIGNATURE PAGE (COORDINATING INVESTIGATOR)

Protocol Number: MCI-186-E05

An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Severe 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 (MTPC) in the form of a Protocol Modification and the appropriate regulatory and Independent Ethics Committee approvals.

Address of Institution: [redacted]

Signed: [redacted]

Print Name: [redacted]

Title: [redacted]

Date: [redacted]

SIGNATURE PAGE (PRINCIPAL INVESTIGATOR)

Protocol Number: MCI-186-E05

An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Severe 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 (MTPC) in the form of a Protocol Modification and the appropriate regulatory and Independent Ethics Committee approvals.

Address of Institution: _____

_____

_____

_____

Signed: _____

Print Name: _____

Title: _____

Date: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
λ_z	Terminal elimination rate constant
AE	Adverse event
AIS	Acute ischaemic stroke
ALP	Alkaline phosphatase
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma 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 quantifiable concentration
$AUCu_{0-\infty}$	Unbound area under the concentration-time curve from time zero to infinity
BLQ	Below the limit of quantification
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CK	Creatine kinase
CL	Total clearance
CLu	Unbound total clearance
C_{max}	Peak drug concentration
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Coefficient of variation percentage
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IV	Intravenous
LDH	Lactate dehydrogenase
LS	Least squares
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MRT	Mean residence time
MTPC	Mitsubishi Tanabe Pharma Corporation
MTPE	Mitsubishi Tanabe Pharma Europe Ltd.
N	Number of subjects
n	Number of observations
PK	Pharmacokinetic(s)
PPK	Population pharmacokinetics
[redacted]	[redacted]
QP	Qualified Person
QTcF	Corrected QT interval using Fridericia's formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach peak concentration
UGT	Uridine diphosphate glucuronosyltransferase
US	United States
V_{ss}	Volume of distribution at steady state
V_Z	Volume of distribution during the terminal phase
WHO	World Health Organisation
WMA	World Medical Association

PROTOCOL SYNOPSIS

Protocol number:	MCI-186-E05
Protocol title:	An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Severe Hepatic Impairment Compared to Subjects with Normal Hepatic Function
Sponsor:	Mitsubishi Tanabe Pharma Corporation (MTPC) 17-10, Nihonbashi-Koamicho, Chuo-ku, Tokyo, 103-8405, Japan EU Representative: Mitsubishi Tanabe Pharma GmbH Willstätter Str. 30, 40549 Düsseldorf, Germany
Coordinating Investigator:	[redacted]
Development phase:	Phase I
Indication:	Not applicable
Investigational Medicinal Product (IMP):	MCI-186 (edaravone): Solution for infusion, 30 mg/100 mL
Reference product:	Not applicable
Treatment regimen:	All subjects will be administered 30 mg MCI-186 over 60 minutes on the morning of Day 1. An infusion time window of ±3 minutes is permitted.
Study duration:	Up to 30 days Day -21 to Day -2: pre-admission Screening Day -1: admission to study centre Day 1: dosing Day 3: discharge from study centre Day 7 (+2 days): Follow-up visit
Objectives:	**Primary Objective:** • To assess the pharmacokinetics (PK) of MCI-186 after a single intravenous infusion of 30 mg/hour in subjects with severe hepatic impairment compared to subjects with normal hepatic function **Secondary Objectives:** • To investigate the safety and tolerability of MCI-186 in subjects with severe hepatic impairment and in subjects with normal hepatic function
Study design:	This is an open-label, single-dose study in male and female subjects with severe hepatic impairment and in male and female subject with normal hepatic function. The study will be conducted in the following two groups: Group 1: Subjects with severe hepatic impairment (Child-Pugh Grade C) Group 2: Healthy subjects with normal hepatic function to individually match Group 1 for age, body weight and gender

Planned number of subjects:	At least 12 subjects will be enrolled to ensure 6 subjects in each group will complete the study.
Subject population:	Male or female subjects with severe hepatic impairment and male or female subjects with normal hepatic function.
Main inclusion criteria:	**All subjects** 1. Able to provide written informed consent to participate in this study after reading the participant information sheet and Informed Consent Form (ICF), and after having the opportunity to discuss the study with the Investigator or designee. 2. Male or female subjects age 18 to 75 years (inclusive) at signature of the ICF. 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 ≥50 kg and a body mass index (Quetelet index) ranging from 18 to 37 kg/m^2 (inclusive) at Screening and Day -1. 5. Female subjects who are: a) postmenopausal for at least 1 year, confirmed by follicle-stimulating hormone assessment (>40 mIU/mL), or b) surgically sterilised (hysterectomy, bilateral oophorectomy or salpingectomy), or c) congenital sterility. Female subjects of child-bearing potential must use a highly effective method of contraception (see Protocol body) from the Screening Visit or at least 2 weeks before IMP administration, until 30 days after IMP dosing. Male subject must practice effective contraception from the time of IMP dosing until 90 days after IMP dosing. Adhering to strict abstinence is considered an accepted contraceptive method. **Hepatic impaired subjects (in addition)** 6. Diagnosis of cirrhosis due to parenchymal liver disease, which is documented in the medical history and physical examination and confirmed by at least one of the following: hepatic ultrasound, computed axial tomography scan, magnetic resonance imaging and/or liver biopsy. A Child-Pugh classification score of 10 to 14 obtained during the Screening period (i.e., within 21 days of IMP administration). 7. Chronic (>6 months) and stable hepatic impairment defined as no clinically significant change in disease status at least 14 days before Screening. 8. Acceptable clinical conditions in the opinion of the Investigator on the basis of a physical examination, medical history, 12-lead electrocardiogram (ECG), vital signs and clinical laboratory tests (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 hyperlipidaemia, etc. may be included. **Healthy subjects (in addition)** 9. Subjects with normal hepatic function confirmed with tests within the normal reference range or results with minor deviations which are not considered by the Investigator to be clinically significant. 10. 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 signs and clinical laboratory tests (biochemistry, haematology, coagulation and urinalysis) at Screening, Day -1 and pre-dose on Day 1.
Main exclusion criteria:	**All subjects** 1. Presence or history of severe allergy to food, or any medical product or relevant excipient that is of clinical significance. 2. Subjects who have previously been 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 12-lead ECG abnormalities, including but not limited to, corrected QT interval using Fridericia's formula (QTcF) of >450 ms (male subjects) or >470 ms (female subjects) at Screening, Day -1 or before dosing. 5. Any other history or condition (surgical or medical) of disease which will increase the risk to the subject, will affect the PK of the study drug, or will otherwise influence the assessments to be made in this study, in the opinion of the Investigator. Subjects who have undergone cholecystectomy may be included. 6. History of drug abuse or tested positive for alcohol or drugs of abuse at Screening and Day -1, excluding drugs which may cause a positive drug or abuse test if medically indicated or prescribed. 7. Subjects who regularly, or on average, drink more than 35 units of alcohol per week (one unit is equivalent to 300 mL of beer, 25 mL of spirits or 150 mL of wine). 8. Presence of active infection requiring antibiotics. 9. Positive test for human immunodeficiency virus antigen/antibody at Screening. 10. Donation of one or more units of blood (450 mL) within 3 months prior to Screening, or plasma in the 7 days prior to Screening, or platelets in the 6 weeks prior to

	Screening, or the intention to donate blood within 3 months after the last Follow-up assessment. 11. Participation in another study within the last month (if single dose), or at least 4 months (if multiple dose), or within 10 times the half-life of the respective drug (whichever is longer) before Screening. For biologics, the minimum period is at least 6 months before Screening, the period of the pharmacodynamic effect, or 10 times the half-life of the respective drug, whichever is longer. 12. Subject is currently taking non-permitted concomitant medication. The subjects with normal hepatic function are restricted from use of any concomitant medications (including paracetamol) unless discussed and agreed with the Sponsor. In subjects with hepatic impairment, the use of prescribed medications is permitted for hepatic or concomitant disease as described in the Protocol body. 13. Not willing to abstain from consumption of coffee, tea, cola, energy drinks or chocolates from admission to the unit (Day -1) to discharge from the unit (Day 3). 14. Uncontrolled, or untreated hypertension defined as a mean of three repeated measurements of systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg. 15. Subjects have estimated glomerular filtration rate <60 mL/min/1.73 m^2 as determined by Modification of Diet in Renal Disease formula. 16. Any condition associated with dehydration. 17. Female subjects: a) who have a positive pregnancy test at Screening or on Day -1. b) who are pregnant, lactating or planning to become pregnant during the study. **<u>Hepatic impaired subjects (in addition)</u>** 18. Subjects with severe ascites or pleural effusion which will, in the opinion of the Investigator, adversely affect the subject's ability to participate in the study. 19. Subjects with severe encephalopathy (Grade III or IV). 20. Subjects with sclerosing cholangitis. 21. Serum albumin <2.0 g/dL. 22. Haemoglobin <10 g/dL. 23. Start of any new medication or any changes to a current dosage within 14 days before IMP administration. **<u>Healthy subjects (in addition)</u>** 24. History or presence of any parenchymal hepatic disease. 25. Positive test for hepatitis B surface antigen or hepatitis C virus antibody.

	26. History of or active suicidal ideation, or suicide attempt as evidenced by positive response to either Question 4 (active suicidal ideation with some intent to act) or Question 5 (active suicidal ideation with specific plan and intent) on the Columbia-Suicide Severity Rating Scale (C-SSRS; Screening Version).
Endpoints:	**Primary Endpoints** **<u>Pharmacokinetic parameters of MCI-186</u>** • 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** **<u>Pharmacokinetic parameters of MCI-186</u>** • Half-life ($t_{½}$) • Time to reach peak concentration (t_{max}) • Terminal elimination rate constant (λ_Z) • Total clearance (CL) • Volume of distribution at steady state (V_{ss}) • Volume of distribution during the terminal phase (V_Z) • Mean residence time (MRT) • Unbound area under the concentration-time curve from time zero to infinity ($AUCu_{0\text{-}\infty}$) • Unbound total clearance (CLu) **<u>Pharmacokinetic parameters of the sulfate conjugate</u>** • C_{max} • $AUC_{0\text{-last}}$ • $AUC_{0\text{-}\infty}$ • $t_{½}$ • t_{max} **<u>Safety and tolerability</u>** • Incidence of adverse events (AEs) and serious adverse events • Physical examination • Vital signs (blood pressure, pulse rate and body temperature) • 12-lead ECG parameters • Laboratory assessments including biochemistry, haematology, coagulation and urinalysis • C-SSRS
Statistical methods:	The planned sample size of 6 evaluable subjects with severe hepatic impairment and 6 evaluable healthy subjects is not based on a power calculation, but is based on the Food and

	Drug Administration recommendation for at least 6 evaluable subjects per group. **Pharmacokinetic Data Analysis** The plasma concentrations of MCI-186 will be summarised using descriptive statistics by group and time point. 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 the 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. **Safety Data Analysis** Where appropriate, continuous variables will be summarised descriptively, using the number of observations, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarised using frequency counts and percentages. Treatment-emergent AEs will be coded using the latest available version of the Medical Dictionary for Regulatory Activities and will be summarised in incidence tables by System Organ Class and Preferred Term. Concomitant medication will be coded using the World Health Organisation Drug Dictionary.

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 (MTPC; the Sponsor). MCI-186 was first approved in 2001 in Japan, under the trade name of RADICUT®, for the treatment of acute ischaemic 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 and in South Korea in December 2015 for the treatment of amyotrophic lateral sclerosis (ALS) based upon a series of clinical studies completed in Japan for ALS. A New Drug Application (NDA 209176) for MCI-186 for the treatment of ALS was approved by the United States (US) Food and Drug Administration (FDA) on 05 May 2017. 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 ischaemic animals (rats), demonstrated effects such as inhibition of cerebral oedema, 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, MCI-186 caused a transient decrease in blood pressure at doses higher than therapeutic doses, and the decrease was not significant in clinical use.

In toxicity studies of bolus injection, the no observed adverse effect level in repeated-dose toxicity studies in rats and dogs were 10 mg/kg/day and 30 mg/kg/day, respectively. From results of toxicity studies, the Sponsor judged that there were no particular significant findings in clinical use.

Pharmacokinetic (PK) studies showed good correlation between dose and peak drug concentration (C_{max}) or area under the concentration-time curve (AUC) in both animals and humans. MCI-186 is rapidly metabolised; 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. For the glucuronide conjugate reaction, multiple uridine diphosphate glucuronosyltransferase (UGT) isozymes including UGT1A9 with the highest contribution are involved. Neither the sulfate nor the glucuronide have radical scavenging activities. MCI-186 and its metabolites are unlikely to inhibit cytochrome P450 (CYP), UGTs and transporters, and to induce CYPs. The protein binding rate of MCI-186 to human serum protein is high (91% to 92%). Protein binding rate of the sulfate and glucuronide are 99% and 36% to 39%, respectively.

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

1.3 Clinical studies

MCI-186 was evaluated in five Phase I studies in healthy subjects in Japan and Europe, eight clinical studies in AIS subjects in Japan, Europe and Korea, three clinical studies in

subarachnoid haemorrhage subjects in Japan and five clinical studies in ALS subjects in Japan.

A single-dose, Phase I study (0.2 to 2.0 mg/kg) in which IV 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 two subjects in the single-dose study, the values were found to have returned to normal in follow-up examinations. The C_{max} and AUC were proportional to dose, half-life ($t_{½}$) and urinary excretion rate were substantially constant regardless of dose, and there was no difference in PK between single dose and repeated doses (Table 1). Thus, no accumulation of MCI-186 in plasma concentration was observed following repeated doses.

Table 1 Pharmacokinetic parameters of unchanged MCI-186 in Japanese healthy male subjects after single or repeated intravenous infusion (once daily for 7 days)*

Parameter	Dose						
	Single dose					Repeated dose (1.0 mg/kg/40 min)	
	0.2 mg/kg/ 40 min	0.5 mg/kg/ 40 min	1.0 mg/kg/ 40 min	1.5 mg/kg/ 40 min	2.0 mg/kg/ 3 hours	First dose	Final dose
Plasma concentration of unchanged MCI-186 at the time of the completion of administration (ng/mL)	223	659	1727	3061	1226	1616	1736
$t_{1/2\alpha}$ (h)	0.17 (0.19)	0.15	0.17	0.17	0.12	0.14	0.14
$t_{1/2\beta}$ (h)	1.45 (1.49)	1.45	0.85	0.81	0.65	0.89	0.78
$t_{1/2\gamma}$ (h)	- -	-	4.50	5.16	4.38	6.01	5.71
AUC (ng•h/mL)	201† (184)†	581†	1537‡	3005‡	3717‡	1474‡	1669‡

* Values are means; N = 5; - indicates not calculated; Data in brackets were calculated from values after the completion of administration; † AUC 0-8 h; ‡ AUC 0-24 h

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 comparable between elderly and adult males (Table 2), and there was no change in urinary excretion. In addition, there was no difference in safety profile between the elderly and adult male subjects, and no notable clinically significant findings.

Table 2 Plasma pharmacokinetic parameters of unchanged MCI-186 after the initial administration of repeated intravenous infusion to Japanese healthy elderly and adult subjects (0.5 mg/kg/30 min × 2 times/day × 2 days) *

Parameter	Healthy adult males	Healthy elderly males
C_{max} (ng/mL)	888 ± 171	1041 ± 106
$t_{1/2\alpha}$ (h)	0.27 ± 0.11	0.17 ± 0.03
$t_{1/2\beta}$ (h)	2.27 ± 0.80	1.84 ± 0.17
$AUC_{0-\infty}$ (ng•h/mL)	742 ± 95	725 ± 74

* Mean ± standard deviation; N = 5

Additionally, the Sponsor performed population pharmacokinetics (PPK) analysis from PK data from five Phase I studies in healthy subjects in Japan and Europe[2]. The PPK analyses demonstrated no difference in PK profiles by race, gender, age or weight between Japanese and Caucasian subjects.

MCI-186 is metabolised 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. The glucuronide is the predominant metabolite in urine. MCI-186 and both the metabolites are excreted into urine. The proportion of MCI-186 excreted in urine is approximately 1% of the dose administered.

In addition to safety data in ALS clinical studies, 1.7 million patients with AIS and 2200 patients with ALS in Japan have been treated with MCI-186, showing an acceptable safety profile. While hepatic and renal disorders were reported in post-marketing in AIS patients, these events were not observed as clinically significant findings in AIS and ALS studies. The package insert for treatment of AIS and ALS in Japan states that MCI-186 is contraindicated in patients with severe renal impairment and should be administered with care in patients with hepatic impairment. Conversely, there are no contraindications or warnings to patients with renal or hepatic impairment in the package insert for treatment of ALS in the US.

The Sponsor is conducting a PK study in subjects with mild or moderate hepatic impairment in Japan (MCI-186-J23). The interim PK data indicate that mild or moderate hepatic impairment may not increase exposure to MCI-186 (Table 3).

[redacted]

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

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 metabolised in the liver and kidney and mainly excreted *via* the kidney into urine. Therefore, the PK of unchanged MCI-186 will be investigated in subjects with severe hepatic impairment. In addition, the PK of metabolised MCI-186 (sulfate conjugate) will be investigated. Although it is inactive, the sulfate conjugate is formed in the liver and present in larger amounts in plasma than unchanged MCI-186 or the glucuronide conjugate.

The tolerability of the dosing regimens 1.5 mg/kg/40 min and 2.0 mg/kg/3 hours were confirmed in a Phase I study (Table 1). 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 half of the approved daily therapeutic dosage for treatment of AIS or ALS.

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 with MCI-186. The presence of severe infection and the implementation of dialysis 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 (percentage) of patients with "MCI-186 related liver injury" was considered to be 25 (20.3%) patients. Among 123 evaluated patients, 104 met the criteria for "evident liver injury" using modified Hy's Law. Of these 104 patients, 86 (82.7%) patients 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, ischaemic 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 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),

alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine 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. In a similar dosing regimen (0.5 mg/kg of MCI-186 IV infusion over 30 min), C_{max} and AUC of unchanged MCI-186 in healthy elderly subjects were 1041 ng/mL and 725 ng•h/mL, respectively (Table 2). 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. Simulated C_{max} and AUC for the ALS regimen were 1049 ng/mL and 1374 ng•h/mL, respectively[2].

The dose in this study is a single dose of 30 mg MCI-186 intravenously administered over 60 minutes. Simulated C_{max} and AUC for the 30 mg dose level in healthy subjects are 470 ng/mL and 600 ng•h/mL, respectively[2]. The Sponsor set the 30 mg dose level to ensure the subjects' safety as the effect of severe hepatic impairment on PK profile is unclear.

In addition, dose proportionality for MCI-186 was assessed by simulation data from a PPK model. The plasma concentrations of MCI-186 following the administration of 10, 30, 60 and 120 mg/hour/body dosing were simulated for 1000 subjects in each dosing group. The PK parameters C_{max} and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) were calculated from the simulated plasma concentration of MCI-186 using a non-compartmental analysis and the analysis of dose proportionality (linearity) was carried out using a power model. The results of the power model are shown in Table 4. From a statistical viewpoint, C_{max} and $AUC_{0-\infty}$ did not exhibit dose-proportionality in the range of 10 to 120 mg as the 95% confidence interval (CI) for the slopes did not include the value 1. Conversely, the regression expressions for Dose-C_{max} and Dose-$AUC_{0-\infty}$ were $Log(C_{max}) = 1.1375*log(Dose)+2.2800$ and $Log(AUC_{0-\infty}) = 1.1595*log(Dose)+2.5216$, respectively. These results imply that when the dose is doubled, C_{max} and $AUC_{0-\infty}$ are increased by 2.20 and 2.32 times, respectively.

Table 4 Analysis of dose-proportionality

Parameter	Slope	95% confidence interval
C_{max}	1.1375	1.1337 - 1.1412
$AUC_{0-\infty}$	1.1595	1.1547 - 1.1643

For the reasons stated above, the PK of MCI-186 is almost linear and the PK of 60 mg MCI-186 infused over 60 minutes can be extrapolated from the results of 30 mg MCI-186 infused over 60 minutes. Therefore, it is possible to evaluate PK in all subjects who will be administered 30 mg of MCI-186.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

2.1.1 Primary objective

The primary objective of this study is to assess the PK of MCI-186 after a single IV infusion of 30 mg/hour in subjects with severe 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 severe hepatic impairment and in subjects with normal hepatic function.

2.2 Study endpoints

2.2.1 Primary endpoints

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

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

2.2.2 Secondary endpoints

The following secondary endpoints will be evaluated during the study:

Pharmacokinetic parameters of MCI-186

- $t_{½}$
- Time to reach peak concentration (t_{max})
- Terminal elimination rate constant (λ_Z)
- Total clearance (CL)
- Volume of distribution at steady state (V_{ss})
- Volume of distribution during the terminal phase (V_Z)
- Mean residence time (MRT)
- Unbound area under the concentration-time curve from time zero to infinity ($AUCu_{0\text{-}\infty}$)
- Unbound total clearance (CLu)

Pharmacokinetic parameters of the the sulfate conjugate

- C_{max}
- $AUC_{0\text{-}last}$
- $AUC_{0\text{-}\infty}$
- $t_{½}$
- t_{max}

Safety and tolerability

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Physical examination
- Vital signs (blood pressure, pulse rate and body temperature)
- 12-lead electrocardiogram (ECG) parameters

- Laboratory assessments including biochemistry, haematology, coagulation and urinalysis
- Columbia-Suicide Severity Rating Scale (C-SSRS; see Appendix 1 in Section 14)

3 STUDY DESIGN

3.1 Overall study design

This is a Phase I, open-label, single-dose study to evaluate the PK of MCI-186 in male and female subjects with severe hepatic impairment (Group 1, n = 6), defined using the Child-Pugh classification, and in male and female subjects with normal hepatic function (Group 2, n = 6). Subjects may be replaced or additional subjects may be enrolled to ensure a minimum threshold of 6 completing subjects per group.

- Group 1: Subjects with severe hepatic impairment (Child-Pugh total score of 10 to 14 [Grade C])
- Group 2: Healthy subjects with normal hepatic function to match Group 1 for age, body weight and gender

All subjects will be administered 30 mg MCI-186 over 60 minutes on the morning of Day 1. An infusion time window of ±3 minutes is permitted.

Order of subject enrolment

Individual matching of healthy subjects will be performed for the subjects with hepatic impairment. Therefore, after the end of study assessments are completed in subjects with hepatic impairment, healthy subjects will be enrolled. Each healthy subject will be individually matched with a hepatic impairment subject with respect to age (±15 years), body weight (±20%) and gender. Matched healthy subjects may be recruited by any study site, not necessarily by the same site which recruited the subject with hepatic impairment.

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 pre-admission Screening period (Day -21 to Day -2)
- A treatment hospitalisation period (Day -1 to Day 3) with single IV infusion of 30 mg MCI-186 over 60 minutes (including an infusion time window of ±3 minutes) on Day 1, and PK blood sampling until 48 hours post-dose. All subjects will be confined to the study centre from Day -1 to Day 3. Safety assessments will be performed until discharge.
- A Follow-up Period (Day 7 +2 days). An end of study assessment will be performed.

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

3.2 Rationale for study design and treatment regimens

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

Both males and females 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 PK. It is considered an appropriate design for the clinical evaluation of the PK, safety and tolerability of MCI-186 in this sub-population of special interest.

3.2.1 Risk:benefit statement

MCI-186 has been evaluated in five Phase I studies in healthy subjects in Japan and Europe, eight clinical studies in AIS subjects in Japan, Europe and Korea, three clinical studies in subarachnoid haemorrhage subjects in Japan and five clinical studies in ALS in Japan.

At present, around 5000 ALS subjects have been treated with MCI-186 in Japan, South Korea and the US, and there is no safety concern regarding hepatic function. While hepatic and renal disorders were reported in post-marketing in AIS patients, these events were not observed as clinically significant findings in AIS and ALS studies. The package insert for treatment of AIS and ALS in Japan states that MCI-186 is contraindicated in patients with severe renal impairment and should be administered with care in patients with hepatic impairment. Conversely, there are no contraindications or warnings to patients with renal or hepatic impairment in the package insert for treatment of ALS in the US.

The following high risk subjects are excluded: subjects 1) who are of advanced age (>75 years) or 2) who present with severe infection. In addition, the dose in this study is a single dose of 30 mg MCI-186 intravenously administered over 60 minutes (including an infusion time window of ±3 minutes). This dose is half 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, ALP, LDH, CK, RBC count and platelet count. The study will be conducted at a study centre which specialises in conducting studies in subjects with hepatic impairment.

This is a PK study in healthy subjects and subjects with severe 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 ultimately guide appropriate use of MCI-186 in the drug labelling.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

The Sponsor does not operate a Protocol waiver system for eligibility criteria.

4.1 Number of subjects

At least 12 subjects will be enrolled to ensure 6 subjects in each group will 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 any study centre. All recruitment material will be approved by the Independent Ethics Committee (IEC) 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. Able to provide written informed consent to participate in this study after reading the participant information sheet and Informed Consent Form (ICF), and after having the opportunity to discuss the study with the Investigator or designee.
2. Male or female subjects age 18 to 75 years (inclusive) at signature of the ICF.
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 ≥50 kg and a body mass index ([BMI] Quetelet index) ranging from 18 to 37 kg/m^2 (inclusive) at Screening and Day -1.
5. Female subjects who are:
   a) postmenopausal for at least 1 year, confirmed by follicle-stimulating hormone (FSH) assessment (>40 mIU/mL), or
   b) surgically sterilised (hysterectomy, bilateral oophorectomy or salpingectomy), or
   c) congenital sterility.

   Female subjects of child-bearing potential must use a highly effective method of contraception (see Section 4.7.5) from the Screening Visit or at least 2 weeks before Investigational Medicinal Product (IMP) administration, until 30 days after IMP dosing. Male subject must practice effective contraception from the time of IMP dosing until 90 days after IMP dosing. Adhering to strict abstinence is considered an accepted contraceptive method.

Hepatic impaired subjects (in addition)

6. Diagnosis of cirrhosis due to parenchymal liver disease, which is documented in the medical history and physical examination and confirmed by at least one of the following: hepatic ultrasound, computed axial tomography scan, magnetic resonance imaging and/or liver biopsy. A Child-Pugh classification score of 10 to 14 obtained during the Screening period (i.e., within 21 days of IMP administration).

7. Chronic (>6 months) and stable hepatic impairment defined as no clinically significant change in disease status at least 14 days before Screening.
8. Acceptable clinical conditions in the opinion of the Investigator on the basis of a physical examination, medical history, 12-lead ECG, vital signs and clinical laboratory tests (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 hyperlipidaemia, etc. may be included.

Healthy subjects (in addition)

9. Subjects with normal hepatic function confirmed with tests within the normal reference range or results with minor deviations which are not considered by the Investigator to be clinically significant.
10. 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 signs and clinical laboratory tests (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 medical product or relevant excipient that is of clinical significance.
2. Subjects who have previously been 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 12-lead ECG abnormalities, including but not limited to, corrected QT interval using Fridericia's formula (QTcF) of >450 ms (male subjects) or >470 ms (female subjects) at Screening, Day -1 or before dosing.
5. Any other history or condition (surgical or medical) of disease which will increase the risk to the subject, will affect the PK of the study drug or will otherwise influence the assessments to be made in this study, in the opinion of the Investigator. Subjects who have undergone cholecystectomy may be included.
6. History of drug abuse or tested positive for alcohol or drugs of abuse at Screening and Day -1, excluding drugs which may cause a positive drugs or abuse test if medically indicated or prescribed.
7. Subjects who regularly, or on average, drink more than 35 units of alcohol per week (one unit is equivalent to 300 mL beer, 25 mL of spirits or 150 mL of wine).
8. Presence of active infection requiring antibiotics.
9. Positive test for human immunodeficiency virus (HIV) antigen/antibody at Screening.

10. Donation of one or more units of blood (450 mL) within 3 months prior to Screening, or plasma in the 7 days prior to Screening, or platelets in the 6 weeks prior to Screening, or the intention to donate blood within 3 months after the last Follow-up assessment.
11. Participation in another study within the last month (if single dose), or at least 4 months (if multiple dose), or within 10 times the half-life of the respective drug (whichever is longer) before Screening. For biologics, the minimum period is at least 6 months before Screening, the period of the pharmacodynamic effect, or 10 times the half-life of the respective drug, whichever is longer.
12. Subject is currently taking non-permitted concomitant medication. The subjects with normal hepatic function are restricted from use of any concomitant medications (including paracetamol) unless discussed and agreed with the Sponsor. In subjects with hepatic impairment, the use of prescribed medications is permitted for hepatic or concomitant disease as described in Section 6.3.1.
13. Not willing to abstain from consumption of coffee, tea, cola, energy drinks or chocolates from admission to the unit (Day -1) to discharge from the unit (Day 3).
14. Uncontrolled, or untreated hypertension defined as a mean of three repeated measurements of systolic blood pressure (SBP) >180 mmHg and/or diastolic blood pressure (DBP) >100 mmHg.
15. Subjects have estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 as determined by Modification of Diet in Renal Disease (MDRD) formula.
16. Any condition associated with dehydration.
17. Female subjects:
    a) who have a positive pregnancy test at Screening or on Day -1.
    b) who are pregnant, lactating or planning to become pregnant during the study.

Hepatic impaired subjects (in addition)

18. Subjects with severe ascites or pleural effusion which will, in the opinion of the Investigator, adversely affect the subject's ability to participate in the study.
19. Subjects with severe encephalopathy (Grade III or IV).
20. Subjects with sclerosing cholangitis.
21. Serum albumin <2.0 g/dL.
22. Haemoglobin <10 g/dL.
23. Start of any new medication or any changes to a current dosage within 14 days before IMP administration.

Healthy subjects (in addition)

24. History or presence of any parenchymal hepatic disease.
25. Positive test for hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCVAb).
26. History of or active suicidal ideation, or suicide attempt as evidenced by positive response to either Question 4 (active suicidal ideation with some intent to act) or Question 5 (active suicidal ideation with specific plan and intent) on the C-SSRS (Screening Version; see Appendix 1 in Section 14).

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 subject becomes pregnant
- Continuing in the study would be detrimental to the subject's safety in the opinion of the Investigator, e.g.,
    - 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 reason(s) 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 electronic case report form (eCRF).

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

Any withdrawal due to an AE or for any safety reason should be assessed for seriousness according to Section 8.2.

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 eCRF. The study centre 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.

4.6 Study stopping criteria

If any subject experiences either a severe AE which the Investigator considers is related to MCI-186, or a severe or serious adverse drug reaction, then the subject is to be immediately withdrawn and no further subjects will be recruited. The withdrawn subject should be followed up as detailed in Section 4.5.

4.7 Lifestyle restrictions

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

4.7.1 Attendance

- Subjects must be available to attend visits according to the Protocol.
- Subjects must be available for overnight stays in the study centre from Day -1 to Day 3.

4.7.2 Alcohol restrictions

- Subjects should refrain from consuming food or drink containing alcohol in the 48 hours before each visit and whilst confined to the study centre.
- Subjects should avoid excessive consumption (>2 units per day) of food or drink containing alcohol at all other times from the Screening Visit until the Follow-up assessment.

4.7.3 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 centre from Day -1 to Day 3.

4.7.4 Smoking

No smoking or using tobacco- or nicotine-containing products (snuff, chewing tobacco, cigarettes, cigars, pipes, e-cigarettes or nicotine replacement products) will be allowed in the study centre from at least 4 hours before dosing to 6 hours after dosing, and from at least 1 hour before scheduled ECG and vital signs examinations until the end of each examination.

4.7.5 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 Visit or at least 2 weeks before IMP administration until 30 days after IMP dosing. Male subjects must be willing and able to practice birth control from the time of IMP dosing until 90 days after IMP dosing.

- **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 or intrauterine system.
  - Established use of oral, injected or implanted 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.
  - True abstinence: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Female subjects must not donate ova for the duration of the study, from the time of the first dose of IMP until 3 months after the last dose of IMP.

- **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:
  - Progesterone-only oral contraception, where inhibition of ovulation is not the primary mode of action.

- Cap, diaphragm or sponge with spermicide.

Male subjects must not donate sperm for the duration of the study, from the time of IMP dosing until 90 days after IMP dosing.

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

- Postmenopausal for at least 1 year, confirmed by FSH assessment (>40 mIU/mL).
- Hysterectomy, bilateral oophorectomy or salpingectomy.
- Congenital sterility.

Subjects must not have unprotected sexual intercourse during the study.

4.7.6 Diet

- While confined to the study centre, subjects will receive standardised meals at scheduled times.
- Subjects should have breakfast on Day 1 after the pre-dose assessment including PK blood sampling and at least 30 minutes prior to the start of IMP administration.
- Lunch on 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 Screening and from 72 hours before the check-in on Day -1.

4.7.7 Physical activity restrictions

- Must not participate in heavy physical training or excessive exercise (e.g., long distance running, weight lifting), or any physical activity to which the subject is not accustomed from 7 days before IMP dosing, during the study and until the Follow-up assessment.

4.7.8 Blood donation

- Subjects must not have donated one or more units of blood (450 mL) in the 3 months prior to Screening, or plasma in the 7 days prior to Screening, or platelets in the 6 weeks prior to Screening.
- Subjects must agree not to donate blood for 3 months after the last Follow-up assessment.

5 STUDY PLAN

Study assessments are summarised in the time and events schedule (Table 5).

Table 5 Time and events schedule

Study Period	**Screening**	**Treatment Hospitalisation**																**Follow-up**
Study Day	**-21 to -2**	**-1**	**1**												**2**		**3**	**7 (+2)**
Time point			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
Informed consent	X																	
Confinement		←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	
Outpatient	X																	X
Inclusion/exclusion criteria	X	X	X															
Demography & medical history	X																	
Physical examination	X	X	X[2]												X[2]		X	X[2]
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																
Biochemistry, haematology, coagulation & urinalysis	X	X													X		X	X
C-SSRS		X													X			
Hepatic impairment assessment (Child-Pugh classification; Group 1 only)	X	X																
eGFR	X	X													X		X	X
Hepatitis B & C and HIV	X																	
Pregnancy test in females	X	X																X
Protein binding blood sampling		X																
IMP administration				←	—	—	→											
PK sampling (blood)[3]			■		■	■	■	■	■	■	■	■	■	■	■	■	■	

Study Period	**Screening**	**Treatment Hospitalisation**															**Follow-up**
Study Day	**-21 to -2**	**-1**	**1**												**2**	**3**	**7 (+2)**
Time point			[redacted]														
AE and concomitant medications	←																→

Abbreviations: AE=adverse event; BMI=body mass index; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; HIV=human immunodeficiency virus; IMP=Investigational Medicinal Product; PK=pharmacokinetic.

1. IMP administration starting time. IMP will be administered over 60 minutes. The permitted infusion time window is ±3 minutes
2. Abbreviated physical examination only
3. The time windows for PK sampling during the study are as follows. All times relate to the infusion start time:
   - pre-dose: -60 to -30 minutes
   - [redacted] ±5 minutes
   - [redacted] +3 minutes from end of infusion
   - [redacted]: ±5 minutes
   - [redacted] ±15 minutes

5.1 Subject informed consent

Prior to performing any study procedures, the Investigator (or designated personnel) 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

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

Subjects will be requested to attend the study centre after a 5-hour fasting period (apart from water). Written informed consent will be obtained before any screening procedures are performed. The following assessments will be performed (refer to Table 5 for further details):

- Written informed consent
- Verify inclusion/exclusion criteria
- Medical history
- Demography
- Physical examination (including height, weight and BMI)
- 12-lead ECG
- Vital signs (including standing and supine blood pressure, pulse rate and body temperature)
- Routine laboratory evaluations (biochemistry; haematology; 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 (Group 1 only)
- eGFR assessment using the MDRD formula
- AE and concomitant medication recording

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

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

Subjects who successfully complete pre-admission Screening will return to the study centre on 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 at Day 1 pre-dose. Eligible subjects will proceed to dosing.

Any subject who does not receive a single dose of IMP will be considered a screen failure (this includes subjects who successfully complete the pre-admission Screening, but fail on study eligibility criteria at admission or Day 1 pre-dose).

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

The following procedures will be performed on Day -1 (refer to Table 5 for further details):

- Verify inclusion/exclusion criteria
- Physical examination (including weight and BMI)
- 12-lead ECG
- Vital signs (including supine blood pressure, pulse rate and body temperature)
- Routine laboratory evaluations (biochemistry; haematology; coagulation; urinalysis; screening for drugs of abuse and alcohol; pregnancy test for females only)
- C-SSRS (see Appendix 1 in Section 14)
- Degree of hepatic impairment by Child-Pugh classification (Group 1 only)
- eGFR assessment using the MDRD formula
- Blood sampling for protein binding
- AE and concomitant medication recording

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

The following procedures will be performed at pre-dose on Day 1 (refer to Table 5 for further details):

- Verify inclusion/exclusion criteria
- Abbreviated physical examination
- 12-lead ECG
- Vital signs (including supine blood pressure, pulse rate and 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 study, will be included into the treatment phase.

A single IV infusion of 30 mg MCI-186 will be administered over 60 minutes on the morning of Day 1. The permitted infusion time window is ±3 minutes.

The following assessments will be performed during the treatment phase (refer to Table 5 for further details):

- Abbreviated physical examination (including weight on Day 2) and physical examination (including weight on Day 3)
- 12-lead ECG
- Vital signs (including supine blood pressure, pulse rate and body temperature)
- Routine laboratory evaluations (biochemistry; haematology; coagulation; urinalysis)
- C-SSRS (Day 2 only; see Appendix 1 in Section 14)
- eGFR assessment using the MDRD formula

- Blood sampling for PK analysis [redacted] all times relate to the infusion start time)
- AE and concomitant medication recording

5.2.3 Follow-up (Day 7 +2 days)

Subjects will return to the study centre on Day 7 for a Follow-up assessment. The following assessments will be performed (refer to Table 5 for further details):

- Abbreviated physical examination (including weight)
- 12-lead ECG
- Vital signs (including supine blood pressure, pulse rate and body temperature)
- Routine laboratory evaluations (biochemistry; haematology; coagulation; urinalysis; pregnancy test for females)
- eGFR assessment using the MDRD formula
- AE and concomitant medication recording

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

5.2.4 Unscheduled visits

An unscheduled visit is defined as any visit to the study centre 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 will take priority over any other scheduled study assessments. Where scheduled study assessments are planned for the same time, the following sequence should be followed: (1) ECG recording; (2) vital signs assessments; (3) physical examination; (4) blood sampling, with PK blood sampling occurring within the windows presented below; and (5) meal (if applicable).

The time windows for PK sampling during the study are as follows:

- pre-dose: -60 to -30 minutes
- [redacted]: ±5 minutes
- [redacted] +3 minutes from end of infusion
- [redacted]: ±5 minutes
- [redacted]: ±15 minutes

All times relate to the infusion start time.

For safety assessments up to 2.5 hours post-dose, a time margin of ±15 minutes is allowed. For all other safety assessments, a time margin of 10% of the elapsed time since last medication dosing is allowed. Pre-dose assessments can be done between the time the subject wakes up and dosing. The order of pre-dose assessments may be adapted if necessary for practical reasons.

6.1 Demography

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

6.2 Medical history

Any significant and relevant past conditions and any current medical conditions prior to Screening will be recorded.

6.3 Medication

Any medication that was stopped prior to administration of IMP will be recorded in the eCRF as prior medication.

Concomitant medication is defined as any medication that is ongoing at the time of dosing or started after administration of IMP, including prescription and over the counter medications. All concomitant medications taken while the subject is participating in the study will be recorded.

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, e.g., acetylsalicylic acid for mild analgesia, or hormonal contraceptives.

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. For subjects with severe hepatic impairment, the use of prescribed medications is permitted as described in Appendix 2 in Section 14. 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 administered within 14 days before Screening and from 14 days before Day -1 (check-in) to Day 3 (discharge).

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

- Antibiotics (e.g., cefazolin sodium, cefotiam hydrochloride, piperacillin sodium, etc.)
- Strong sulfotransferase inducers or inhibitors (e.g., mefenamic acid, acetaminophen and ibuprofen)
- Strong UGT inducers or inhibitors (e.g., diclofenac sodium and verapamil hydrochloride)

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 is based 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 categorised into mild, moderate and severe as summarised in Table 7. At Screening, a Child-Pugh classification score of 10 to 14 for subjects with severe hepatic impairment is required for entry into the study. Child-Pugh classification will also be assessed at Day -1, and this value will be used in the PK assessments described in Section 10.3.5.1.

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 (μmol/L)	<34	34 – 50	>50
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 at the study centre 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 glomerular filtration rate

GFR will be estimated using the MDRD formula[7].

$$eGFR\ (mL/min/1.73\ m^2) = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.212\ \text{if African American})$$

S_{cr}: serum creatinine.

6.6 Pharmacokinetic assessments

6.6.1 Collection of blood samples for pharmacokinetic analysis

Blood samples will be collected *via* cannulation or direct venepuncture in a suitable forearm vein at the times indicated in Table 5. The actual date and time of each blood sample will be recorded in the source documents and eCRF.

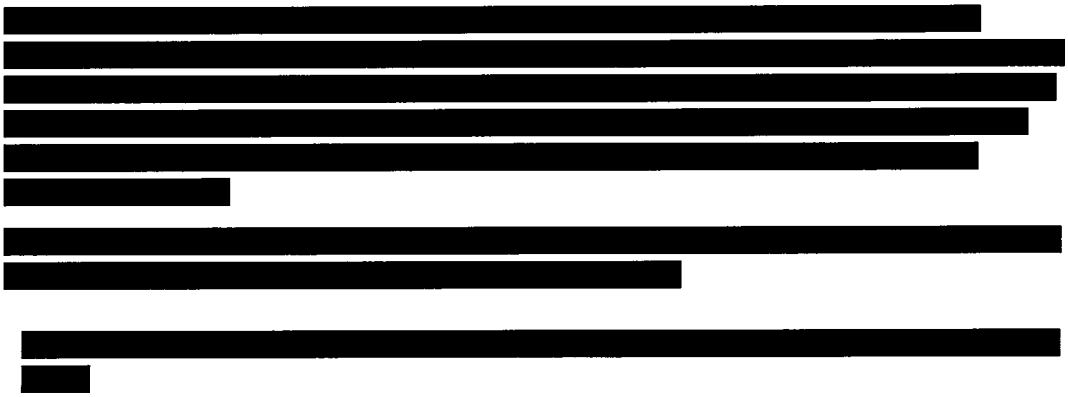
Pharmacokinetic analysis of MCI-186 and its metabolite

[redacted]

Contingency samples will be shipped at the request of the Sponsor.

***In vitro* plasma protein binding of MCI-186 and its metabolite**

A blood sample will be taken for the determination of *in vitro* plasma protein binding of MCI-186 and its metabolite at Day -1 to avoid the effect of the stabiliser included in the collection tube for the MCI-186 and MCI-186 metabolite samples.



The report of *in vitro* plasma protein binding will be reported separately from the Clinical Study Report (CSR).

6.7 Safety assessments

Please refer to Section 8 for details of AE management.

6.7.1 Physical examination

At the times indicated in 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 Table 5. Height will be measured once only (at Screening). The BMI will be calculated using the standard formula at Screening and Day -1.

Body mass index calculation:

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

The abbreviated physical examination will consist of a routine assessment of the following body systems: general appearance, cardiovascular, respiratory and abdominal.

6.7.2 Vital signs

At the times indicated in Table 5, subjects will undergo an assessment of SBP and DBP using an automatic blood pressure recording device with an appropriate cuff size after the subject has rested for at least 5 minutes in a supine position. Three 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 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' or 'abnormal not clinically

significant'. Clinically significant abnormalities will be reported as AEs. Repeat measurements will be performed if needed.

6.7.3 Electrocardiogram

At the times indicated in 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 (QTcF) will be calculated automatically according to Fridericia's formula. In case of results >450 ms in male subjects or >470 ms in female 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' or 'abnormal not clinically significant'. Clinically significant abnormalities 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' or 'abnormal not clinically significant'. Clinically significant abnormalities will be reported as AEs.

Table 8 Routine laboratory evaluations

Haematology:	
Haemoglobin	Mean corpuscular haemoglobin
Haematocrit	Mean corpuscular haemoglobin concentration
Platelet count	Mean corpuscular volume
Red blood cell count	White blood cell count and differential
Biochemistry:	
Alkaline phosphatase	Cholesterol
Aspartate aminotransferase	Triglycerides
Alanine aminotransferase)	High density lipoprotein-cholesterol
Gamma-glutamyl transpeptidase	Low density lipoprotein-cholesterol
Potassium	Protein (total)
Sodium	Albumin
Chloride	Creatine kinase
Inorganic phosphate	Creatinine
Glucose	Follicle-stimulating hormone[1]
Urea	Human chorionic gonadotrophin[2]
Bilirubin (direct and total)	
Coagulation:	
Prothrombin time	Activated partial thromboplastin time
International normalised ratio	
Urinalysis:	
Specific gravity, pH, protein, glucose, ketones, urobilinogen, human chorionic gonadotrophin[2]	
Microscopic examination[3]	
Serology:	
Hepatitis B surface antigen	Human immunodeficiency virus antigen/antibodies
Hepatitis C virus antibody	
Drugs of abuse screen:	
Methadone, cocaine, barbiturates, tetrahydrocannabinol, benzodiazepines, amphetamines, opiates, breath alcohol	

[1] Females only; performed at Screening only
[2] Females only; a serum pregnancy test will be performed at Screening and a urine pregnancy test at all other time points
[3] Performed only if required, based on urinalysis results

Blood samples will be analysed by local laboratories using standard methods. Urine tests will be performed by study centre personnel using commercially available kits. Procedures for the handling of samples will be described in full in a separate document.

6.7.5 Columbia-Suicide Severity Rating Scale

The C-SSRS will be performed at the time points indicated in Table 5.

The C-SSRS questionnaires (Screening/Baseline and Since Last Visit) are presented as an appendix in Section 14.

6.8 Total blood volume

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

Table 9 Blood volumes

Procedure	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
Pharmacokinetics	4	15	60
Protein binding	15	1	15
		Overall total	**142**

Additional or repeat safety laboratory samples may be taken during the study if required by the Investigator. The maximum volume to be drawn from each subject, including re-screening, will be approximately 200 mL.

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 (edaravone) infusion
Dosage form	Solution for infusion.
Description	Clear and colourless sterile solution for intravenous infusion in single-dose polypropylene bags, each overwrapped with polyvinyl alcohol secondary packaging containing an oxygen absorber and oxygen indicator.
Strength	30 mg / 100 mL
Storage conditions	Store at up to 25°C. Protect from light. Store in overwrapped package to protect from oxygen degradation until time of use. The oxygen indicator will turn blue or purple if the oxygen has exceeded acceptable levels. Once the overwrap package is opened, use within 24 hours.

The MCI-186 solution for infusion bags have been manufactured by [redacted].

[redacted] will import the MCI-186 solution for infusion bags into the European Union, perform identification testing and issue a Qualified Person (QP) release certificate. The Sponsor will provide the necessary documentation to show that the infusion bags have been manufactured and tested according to Good Manufacturing Practice (GMP) together with a Batch Certificate, Certificates of Analysis and a Transmissible Spongiform Encephalopathy Statement.

[redacted] will apply a label to the outer blister surface of the IMP infusion bag, repackage the blister into a tertiary container, label each container, QP certify the IMP and ship the IMP to the Investigational site/s. [redacted] will also provide additional labels to be applied directly on to the infusion bags, just prior to administration. All labelling will comply with applicable regulatory requirements. The packaging and labelling will be performed and documented according to GMP by [redacted].

7.1.1 Compliance

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

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

7.1.2 Shipping, receipt, handling and storage

IMP will be shipped from [redacted] to the study centre/s in temperature-controlled shipping systems.

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

At the study centre, the IMP must be stored below 25°C and protected from light 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 IMP will be dispensed by the Investigator or designee. A record of the IMP dispensed to each subject will be maintained by the Investigator or designee in a study-specific IMP dispensing form. Any opened overwrapped infusion bags must be used within 24 hours. Each bag must be allocated to only one subject.

Subjects will be administered an IV infusion of 100 mL (30 mg of MCI-186) as one 30-mg MCI-186 bag over 60 minutes in the morning of Day 1 by the Investigator or designee. An infusion time window of ±3 minutes is permitted.

7.1.4 Accountability, returns and destruction

During the study, the Investigator or designee will record the quantities of IMP dispensed and returned in a study-specific IMP dispensing form. 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 centre until permission has been given by the Sponsor for it to be returned to [redacted] for destruction. Authorisation to return the IMP to [redacted] will only be given following completion and review of all IMP accountability records and resolution of any discrepancies on-site.

[redacted] will arrange for all used IMP and packaging to be destroyed once permission has been given by the Sponsor.

Authorisation to destroy the IMP will usually be given when the CSR is signed, or as instructed by the Sponsor. Confirmation of destruction will be provided to the Sponsor.

7.2 Subject identification

Each subject will be assigned a unique Screening Number at the Screening Visit. At admission into the study, each subject will receive a unique Subject Number. Both the Screening Number and the Subject Number will be documented in the subject's source documents. The Subject Number will be used to identify subjects on IMP labels and other documentation.

Subjects who are withdrawn for non treatment-related reasons may be replaced at the discretion of the Sponsor and Investigator. The substitute subject will receive the same treatment assigned to the subject he/she replaces. Subjects withdrawn as a result of an AE(s) with causality possibly related to the IMP will not be replaced.

A list identifying the subjects by their Screening and Subject numbers will be kept at the study centre.

7.3 Procedures for assigning subjects to treatment groups

The subjects will be assigned to one of two treatment groups at Day -1. Subjects with severe hepatic impairment (Child-Pugh Grade C) will be assigned to Group 1 and subjects with normal hepatic function will be assigned to Group 2. Subjects in Group 2 will be enrolled to match Group 1 for age, body weight and gender.

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 Follow-up Period will be recorded in the eCRF. Even if the AE is assessed by the Investigator as not related to IMP, its occurrence must be recorded in the source documents and eCRF. 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 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
- Is a congenital anomaly or birth defect
- Is an important medical event

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 or 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 judgement 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).

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 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 eCRF. 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 are 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 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 Follow-up Period or the withdrawal of the subject from the study must be notified to [redacted] using the paper SAE 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 reporting contact for SAEs is as follows:

[redacted]

In case of any email problems, the SAE form will be sent to [redacted] Drug Safety Center [redacted] *via* fax to:

Fax: [redacted]

Reports of pregnancy, although <u>not</u> 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 and IECs. The Investigator will be responsible for informing the local IEC of 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. If the outcome or course of the pregnancy involves an SAE (e.g., a congenital anomaly), then a paper SAE form 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 stabilised 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 edaravone Investigator's Brochure[1].

8.11 Overdose

All IMP will be administered by designated qualified study personnel at the study centre who will oversee the administration of all IMP, so an overdose is unlikely. Any subject who does receive an overdose should be given the standard medical care.

If the subject takes a dose which is greater than that specified in the Protocol (with or without associated symptoms), this must be reported to [redacted] immediately or within 24 hours of awareness *via* a paper 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 eCRFs and will be substantiated by source documents (such as laboratory reports, medical records or ECGs) at the study centre. All relevant data will be transcribed into the eCRF 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 eCRF and the eCRF will be considered the source document.

Prior to the start of the study, the Investigator will complete a Delegation of Responsibility List. The Sponsor will provide training for completion of the eCRF. The eCRF will be completed according to guidelines provided by the Sponsor or its designee in writing, electronically and/or verbally.

Completed eCRFs will be reviewed by the Study Monitor for the study to ensure data accuracy, completeness and consistency. Any discrepancies found during the eCRF 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 (or his/her designated personnel).

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 electronically sign and date a declaration on the eCRF 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 data collected in the eCRF will be returned to the Sponsor, and an electronic copy will be retained by the Investigator.

9.2 Case report form completion

The eCRF will be presented in an electronic casebook comprising a series of electronic forms. The Subject Number should always be indicated and date (and time, if applicable) of each assessment should be entered in the eCRF.

The eCRFs must be completed in a timely manner so that this does not delay the ongoing data validation, review and quality control. The final, completed eCRF for each subject must be electronically signed and dated by the Investigator on the appropriate eCRF to signify that he/she has reviewed the electronic casebook and certifies it to be complete and accurate.

9.3 Data processing

The data collected in the eCRFs 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 centre 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 World Health

Organisation (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 6 evaluable subjects with severe hepatic impairment and 6 evaluable healthy subjects is not based on a power calculation, but is based on the FDA recommendation for at least 6 evaluable subjects per group.

In total, 12 subjects will be enrolled to ensure 6 subjects per group complete the study.

10.2 Analysis sets

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

Safety analysis set:	All subjects who receive 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

The statistical analysis will be performed using SAS® Version 9.2 or higher.

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 summarised by group and time point, if appropriate. Unless otherwise stated, continuous data will be summarised descriptively using N (number of subjects), n (number of subjects with observations), mean, standard deviation (SD), minimum, median and maximum. Categorical data will be summarised using frequency tables (frequency and percentage).

The PK parameters of MCI-186 and its metabolite in plasma will be determined from individual concentration-time data by non-compartmental analysis methods using Phoenix® WinNonlin® ver.6.3 or higher.

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 including age, sex, height, weight and race will be summarised by each group and listed by subject. Medical history will be listed by subject. Age will be calculated as the integer difference in years from date of birth to informed consent date.

The number of subjects screened, and the number of subjects in each analysis population will be presented.

10.3.4 Analysis of primary endpoints

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

- C_{max}
- $AUC_{0\text{-last}}$
- $AUC_{0\text{-}\infty}$

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 summarised by group with mean, median, geometric mean, minimum value, maximum value, SD and coefficient of variation percentage (CV%).

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

Additional analyses may be described in the 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. The actual, exact sampling times in relation to dosing will be used. For the calculation of PK parameters, concentrations BLQ will be imputed with a value of zero.

Pharmacokinetic parameters of MCI-186

- $t_{½}$
- t_{max}
- λ_z
- CL
- V_{ss}
- V_z
- MRT
- $AUCu_{0\text{-}\infty}$
- CLu

Pharmacokinetic parameters of the metabolite

- C_{max}
- $AUC_{0\text{-last}}$
- $AUC_{0\text{-}\infty}$
- $t_{½}$
- t_{max}

Individual and mean plasma concentration versus time curves will be plotted for each group 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 (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 for each group. For the calculation of the summary statistics except for

geometric mean and geometric CV%, concentration values reported as BLQ will be set to zero. For the calculation of geometric mean and geometric CV%, concentration values reported as BLQ will be set to half of the lower limit of quantification.

The PK parameters will be summarised. 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.

The following scatter plots will be produced for each group: C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and $AUCu_{0\text{-}\infty}$ of MCI-186 and its metabolite versus Child-Pugh score, albumin, bilirubin, prothrombin time and eGFR with regression line.

Statistical analysis will be used to estimate the ratio of mean PK parameters of the severe hepatic impairment group with respect to the normal hepatic function group. The C_{max} $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ of MCI-186 and its metabolite for the statistical analysis will be the log-transformed estimated AUCs and C_{max}. An analysis of variance model that includes hepatic function as fixed effects, will be used to estimate the least squares (LS) means and intersubject variance. Using these estimated LS means and intersubject variance, the point estimate and 90% CIs for the difference in means on a log scale between severe hepatic impairment group and the normal hepatic function group will be constructed. The limits of the CIs will be re-transformed using antilogarithms to obtain 90% CIs for the ratios of the mean C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ of MCI-186 and its metabolite between each impaired hepatic function group and the normal hepatic function group.

Only the data from subjects who completed the study will be included in the statistical analysis. If one PK 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 PK parameter.

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 summarised descriptively. There will be no formal statistical analysis of the safety data. In general, safety data will be summarised by group and day, as appropriate.

10.3.5.3 Adverse events

Adverse events will be coded using MedDRA (version 20.0 or later). A by-subject AE data listing including start/stop times, verbatim term, Preferred Term, System Organ Class (SOC), 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 TEAEs by SOC and Preferred Term
- Summary of TEAEs by SOC, Preferred Term and severity of event
- Summary of TEAEs by SOC, Preferred Term and relationship to treatment

The above TEAE 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 summarised (N, n, mean, SD, median, minimum and maximum) at each time point by group.

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 summarised (N, n, mean, SD, median, minimum and maximum) at each time point. 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 Columbia-Suicide Severity Rating Scale

Data from the C-SSRS assessments will be listed by subject.

10.3.5.7 Prior and concomitant medication

Prior and concomitant medication will be coded according to the WHO Drug Dictionary (latest version). Prior and concomitant medications will be listed by subject and group, including the Preferred Term.

Prior medication is any medication that was stopped prior to administration of IMP. Concomitant medication is any medication that is ongoing at the time of dosing or started after administration of IMP, including prescription and over the counter medications.

10.3.5.8 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 for this study.

10.3.7 Interim analysis

Not applicable for this 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 Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines. 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

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.

In the event that a subject is legally incompetent, the enrolment of such a subject should be in accordance with all applicable laws, and consent sought by the Investigator from the subject's legally authorised representative.

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 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 centre.

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 emphasise 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 IEC. The study centre 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 Ethical and regulatory approval

The study is conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP as described in:

1. Declaration of Helsinki, concerning medical research in humans (Adopted by the 18th World Medical Association [WMA] General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013).
2. ICH Harmonised Tripartite Guidelines for GCP 1996.
3. Directive 2001/83/EC, The Community Code Relating to Medicinal Products for Human Use.
4. Directive 2001/20/EC, The Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use (The Clinical Trials Directive).

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, all IEC, 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 IEC(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 regulatory authorities and IECs in the form of Protocol Modifications. Protocol Modifications requiring IEC approval may be implemented only after a copy of the IEC's approval/favourable opinion letter has been transmitted to the Sponsor and regulatory authority approval has been obtained (if required). Protocol Modifications that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor, regulatory authority and/or IEC 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. Depending on the nature of the deviation, this may be reported to the appropriate regulatory authority and IEC.

11.2.3 Source document requirements and document access during the study

The Investigator must retain a comprehensive and centralised filing system of all study-related documentation (including, but not limited to: essential documents, copies of

Protocols, eCRFs, 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, IEC reviews and regulatory inspections providing direct access to source data/documents.

11.2.4 Study records retention

Study-related documentation must be kept for at least 25 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 centre, 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 centre. 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 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 centre 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

Authorised representatives of the Sponsor, IEC 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 a study centre 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 study centre 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.

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 IEC, and providing the reason(s) for the suspension or termination of the study.

For all subjects, the Follow-up 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 eCRF. The study centre 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 centre 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 study centre

The Sponsor may at any time, at its sole discretion, discontinue the study centre 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 centre is terminated for non-compliance, appropriate regulatory authorities will also be notified by the Sponsor.

For all subjects, the Follow-up 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 eCRF. The study centre personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required Follow-up assessments.

In addition, all general study centre 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

Please refer to the written study information given to the subject.

12 DISCLOSURE OF DATA

12.1 Confidentiality

A Subject Screening and Enrolment Log will be completed at each study centre for all subjects who signed an ICF. A Subject Identification Log, documenting the subjects' names, will be completed and retained at each study centre 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 IEC 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 eCRFs 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 Investigator's right to publish or present any information on the study, and publication procedures to be followed, will be defined in the study centre agreement.

13 REFERENCES

1. Errata of edaravone Investigator's Brochure ver. 21, 05 July 2018 (including full version of Investigator's Brochure ver. 21, 29 June 2018).
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 labelling. 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;13:118-22.
6. Hirano M. Clinical evaluation of liver injury in patients with acute ischaemic brain stroke treated with edaravone. Hepatol Res. 2011;41:142-50.
7. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247-54.

14 APPENDICES

Appendix 1 Columbia-Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past__ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

 C-SSRS—Baseline Screening (Version 1/14/09) Page 1 of 2

SUICIDAL BEHAVIOR ***(Check all that apply, so long as these are separate events; must ask about all types)***	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts ____ **Yes No** ☐ ☐	**Yes No** ☐ ☐ Total # of Attempts ____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted ____	**Yes No** ☐ ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted ____	**Yes No** ☐ ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐	**Yes No** ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy; somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____

 C-SSRS—Baseline Screening (Version 1/14/09)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say. *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____

Type # (1-5) *Description of Ideation*

Most Severe

Frequency ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability ____
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents ____
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

C-SSRS—Since Last Visit (Version 1/14/09)
Page 1 of 2

SUICIDAL BEHAVIOR ***(Check all that apply, so long as these are separate events; must ask about all types)***	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	**Most Lethal Attempt Date:**
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

Appendix 2 Concomitant medication

Allowed drugs:

- Furosemide
- Ursodeoxycholic acid
- Taurine
- Shousaikoto
- LAC-B (Bifidobacterium)
- Omeprazole
- Monoammonium glycyrrhizinate, glycine, L-cysteine hydrochloride hydrate
- Monoammonium glycyrrhizinate, glycine, DL-methionine
- Azosemide
- Spironolactone
- Tolvaptan
- Glutathione
- Flavin Adenine Dinucleotide Sodium
- Rebamipide
- Teprenone
- Polaprezinc
- Sodium Alginate
- Famotidine
- Lafutidine
- Rabeprazole
- Esomeprazole
- Lansoprazole
- Vonoprazan
- Mosapride
- L-Isoleucine, L-leucine, L-valine
- L-isoleucine, L-leucine, L-lysine hydrochloride, L-threonine, L-valine, L-arginine hydrochloride, L-histidine monohydrochloride, L-tryptophan, gelatin, rice bran oil, dextrin, retinol palmitate, ergocalciferol, bisbentiamine, riboflavin, pyridoxine hydrochloride, cyanocobalamin, folic acid, sodium ascorbate, tocopherol acetate, phytonadione, calcium pantothenate, nicotinamide, biotin, choline bitartrate, magnesium sulfate hydrate, calcium glycerophosphate, potassium phosphate, sodium ferrous citrate, cupric sulfate, zinc sulfate hydrate, potassium iodide, manganese sulfate, potassium chloride, manganese sulfate
- L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-threonine, L-tryptophan, L-valine, L-alanine, L-arginine, L-aspartic acid, L-histidine, L-proline, glycine
- Amlodipine
- Candesartan cilexetil
- Telmisartan
- Atenolol
- Benidipine
- Valsartan
- Irbesartan
- Cilnidipine
- Azilsartan
- Nifedipine
- Insulin

- Sitagliptin
- Alogliptin
- Metformin
- Lamivudine
- Adefovir pivoxil
- Daclatasvir
- Asunaprevir
- Ledipasvir, sofosbuvir
- Lactulose
- Rifaximin
- Magnesium Oxide
- Sodium picosulfate hydrate
- Sennoside A, B
- Pravastatin
- Rosuvastatin
- Atorvastatin
- Ezetimibe
- Allopurinol
- Flunitrazepam
- Etizolam
- Brotizolam
- Zolpidem
- Lactomin、clostridium butyricum、bacillus mesentericus
- Febuxostat
- Aspirin (acetylsalicylic acid)
- Edoxaban
- Loratidine
- Fexofenadine hydrochloride
- Pancreatic digestive enzymes, aspergillus producing digestive enzymes, bacterial lipase, berizym
- Menatetrenone
- Loxoprofen sodium hydrate
- Levodopa
- Carbidopa hydrate
- Benserazide hydrochloride
- Pregabalin
- L-carbocisteine
- Tramadol hydrochloride
- Glucose
- Thiamine disulfide, pyridoxine hydrochloride, hydroxocobalamin acetate
- Purified sodium hyaluronate
- Pirenoxine
- Cyanocobalamin
- Pranoprofen
- Brinzolamide, timolol maleate
- Prednisolone
- Levothyroxine sodium hydrate
- Eldecalcitol
- Chlordiazepoxide
- Methocarbamol

- Sodium gualenate hydrate
- Heparinoid
- Pantoprazole

Not permitted during hospitalisation:

- Verapamil
- Zanthoxylum fruit, ginseng, processed ginger, koi
- Cefazolin sodium
- Cefotiam hydrochloride
- Piperacillin sodium
- Mefenamic acid
- Acetaminophen
- Ibuprofen
- Diclofenac sodium
- Shakuyakukanzoto (glycyrrhizic acid, paeoniflorin)
- Adenosine triphosphate disodium hydrate

Not permitted within 14 days before Screening and from 14 days before Day -1 (check-in) to Day 3 (discharge):

- Albumin preparation

Other concomitant medication will be discussed with the Sponsor.