Statistical Analysis Plan

Protocol Number: MT-186-J20

Dose Finding Study of MCI-186 in Acute Ischemic Stroke

Version Number: 02.00
Date: 19 July, 2018
NCT number: NCT03346538

STATISTICAL ANALYSIS PLAN

Protocol No.	MCI-186-J20
Protocol Title	Dose Finding Study of MCI-186 in Acute Ischemic Stroke
Version History	Version 01.00 First approved version / 17 July, 2018 Version 02.00 First approved version / 19 July, 2018
Author	[redacted]

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Dose Finding Study of MCI-186 in Acute Ischemic Stroke

PREPARED BY: *Mitsubishi Tanabe Pharma Corporation*

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APPROVAL FORM

STATISTICAL ANALYSIS PLAN

Protocol No.	MCI-186-J20
Protocol Title	Dose Finding Study of MCI-186 in Acute Ischemic Stroke
Version	02.00
Author(s)	[redacted]
Position	Biostatistics Group, Data Science Depaetment Ikuyaku. Integrated Value Development Division
Signature	[redacted]
Date	[redacted]

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

REVIEWED BY:

MTPC Statistics Reviewer

Name: [redacted] Date: [redacted] Signature: [redacted]

Position:
Responsible STAT

APPROVED BY:

MTPC Statistics Approver

Name: [redacted] Date: [redacted] Signature: [redacted]

Position:
Head of Regional STAT

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ABBREVIATIONS

UPDATE THE LIST AS APPROPRIATE

AE	:	adverse event
BI	:	Barthel Index
CRF	:	case report form
DP	:	decimal places
ECG	:	electrocardiogram
eCRF	:	electronic case report form
FAS	:	full analysis set
FIM	:	Functional Independence Measure
IAO	:	international agreed order
IMP	:	investigational medicinal product
MedDRA	:	medical dictionary for regulatory activites
mRS	:	modified Rankin Scale
NIHSS	:	National Institutes of Health Stroke Scale
PT	:	preferred term
QC	:	quality control
SAP	:	statistical analysis plan
SAE	:	serious adverse event
SAF	:	safety population
SD	:	standard deviation
SOC	:	system organ class
TEAE	:	treatment emergent adverse event
WHO	:	World Health Organisation

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol version 01.01 dated 1 August 2017. The plan covers statistical analysis, tabulations and listings of efficacy and safety data to investigate the efficacy and safety of MCI-186 (bolus followed by 72-hour continuous infusion) in acute ischemic stroke patients through a double-blind, parallel-group comparison with the existing MCI-186 dosing regimen as the control.

The SAP is prepared by Mitsubishi Tanabe Pharma Corporation(MTPC), Data Science Department. The statistical analyses and production of the outputs described in the SAP will be conducted and QC checked by [redacted] Medical Development Business Department2 SAS Consulting Group, using SAS® 9.3 or later Software. The final analyses and outputs will be approved by Mitsubishi Tanabe Pharma Corporation, Data Science Department.

MTPC has early decided to stop subjects's recruitment based on internal decision. Therefore, the planned sample size will not be completed so that this plan will be executed based on a limited available sample size. The finding for this statistical analysis will lead to exploratory results.

2. STUDY OBJECTIVE(S) AND ENDPOINTS

2.1 Study Objective(s)

To investigate the efficacy and safety of MCI-186 (bolus followed by 72-hour continuous infusion) in acute ischemic stroke patients through a double-blind, parallel-group comparison with the existing MCI-186 dosing regimen as the control.

2.2 Primary Efficacy/Safety Endpoint(s)/Assessments

- Primary endpoint

NIHSS (change over the 7 days from onset)

2.3 Secondary Efficacy/Safety Endpoint(s)/Assessments

- Secondary endpoints

(1) NIHSS (Day 4, Day 7, Day 10, Day 14, after 3 weeks, at discharge, after 3 months)

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

(3) BI (Day 14, after 3 weeks, at discharge, after 3 months)

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

(5) Start of rehabilitation

(6) Duration of hospitalization

(7) Cranial imaging diagnosis

2.4 Safety Assessment(s)

- Safety endpoints

(1) Adverse events and adverse reactions

(2) Neurological testsassessments

(3) Common clinical laboratory tests

(4) Vital signs

(5) Standard 12-lead ECG

2.5 Pharmacokinetics Endpoint(s)/Evaluation(s)

Not applicable in the study.

2.6 Pharmacodynamics Endpoint(s)/Evaluation(s)

Not applicable in the study.

2.7 Other Endpoint(s)/Evaluation(s)

- Exploratory endpoint

[redacted]

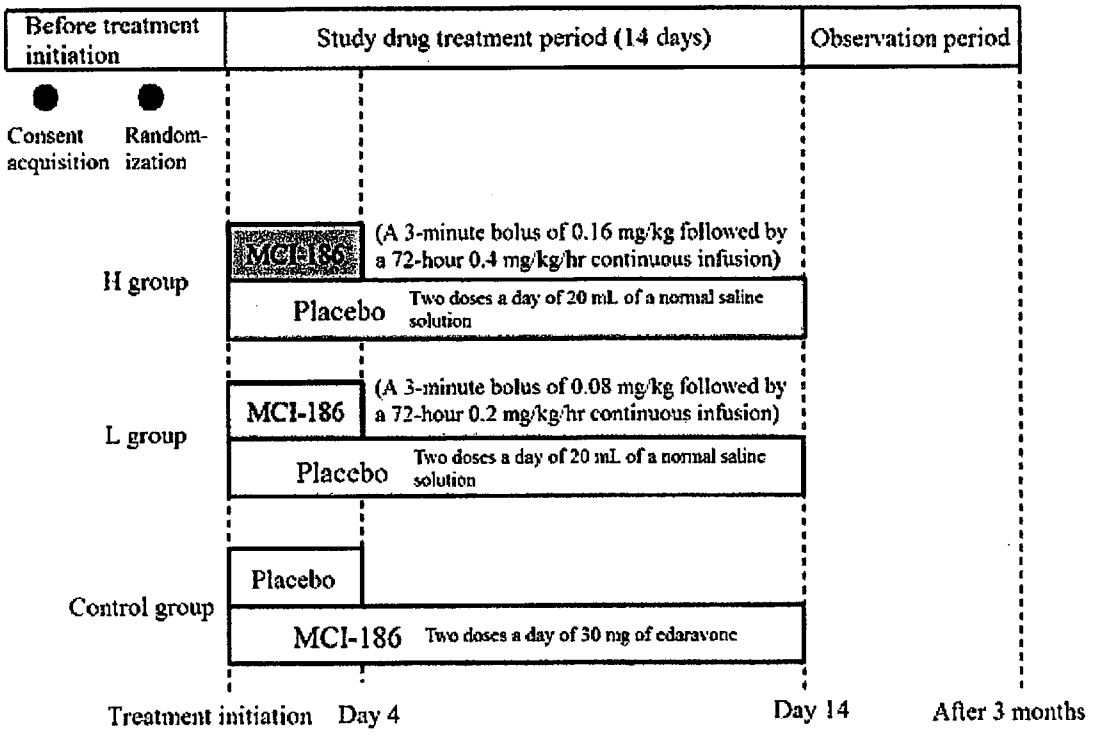
3. STUDY DESIGN

3.1 Study Design

Phase of study : Phase 2

Study type : Confirmatory study (planned)

Multicenter, randomized, double-blind, parallel-group study with the approved dosing regimen as the control



Rationale

This study was designed as a parallel-group comparative study with the existing dosing regimen as the control in order to objectively investigate the efficacy and safety of the 72-hour continuous infusion dosing regimen. In addition, in order to minimize rater bias, a double-dummy method will be used to administer the investigational product, and the study will be conducted using a randomized, double-blind method.

3.2 Schedule of Study Procedures

Study assessments are summarized in the Time and events schedule (Table 1).

Table 1: Assessment and Observation Schedule

Assessment Time Point	Before Treatment Initiation			Study Drug Treatment Period								Observation period		
	Consent	Confirmation of suitability	Registration	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 10	Day 14 or study drug treatment period discontinuation[a]	After 3 weeks[b]	At discharge	After 3 months[c] or at observation period discontinuation
Allowable Range									±1 day	±1 day	+1 day	±2 days	−1 day	±8 days (+8 days)
Consent acquisition	●													
Subject background		●												
Registration/allocation			●											
Study drug treatment				72-hour continuous infusion										
				Twice a day for 14 days[d]										
NIHSS		●		Assessments performed every day for 7 days after treatment initiation						●	●	●	●	●
mRS[e]		●[f]										●	●	●
BI											●	●	●	●
FIM												●	●	●
[redacted]											●	●	●	●
Diagnostic imaging		DWI T2*WI FLAIR MRA					DWI[g] T2*WI[g]				DWI T2*WI			FLAIR
Neurological assessments						●[h]					●	●	●	●
Standard 12-lead ECG		●					●[i]							
Vital signs		●					●[i]		●		●			
Clinical laboratory tests (centralized measurements)		●					●[i]		●	●	●	●	●	
Clinical laboratory tests (site measurements)		●[j]		Measured every day for 5 days after treatment initiation[k]										
PGx blood sample collection				● (Blood samples will be collected during the study from subjects who have consented to having blood samples collected for genetic analysis)										
Adverse events				←										
Concomitant medications		←												

a) If the study is discontinued during the study drug treatment period, the tests that are stipulated should be conducted at study drug treatment period discontinuation will be conducted, and whenever possible subject safety will be evaluated at 3 months after onset.

b) In this study, "after 3 weeks" is defined at Day 22. If a subject is discharged within 3 weeks after treatment initiation, then the tests that are stipulated should be performed at discharge will be performed, and the tests that are scheduled for after 3 weeks will not be necessary.

c) In this study, after 3 months is defined as Day 85. If the study is going to be discontinued during the observation period, then the tests that are stipulated should be conducted at observation period discontinuation will be conducted, and subject safety will be assessed after 3 months whenever possible.

d) Twice a day, at morning and at night, for 14 days. As a rule, the drug is administered for 14 days. However, in the period after the treatment has been administered for 7 days following treatment initiation and the NIHSS assessments have been completed, treatment may be stopped only if the (sub)investigator determines that the neurological symptoms associated with the primary disease have returned to their baseline levels, the patient's condition has stabilized, and that consequently continuing to administer the study drug would not be clinically meaningful, and administering the drug would only be detrimental for the subject in that it would restrict the

subject's freedom. (the subject may not be discharged).

e) The mRS assessments will be performed using the Japanese-language version of the mRS questionnaire (Cerebrovasc Dis 2006;21:271-278) (Attachment 2: mRS Questionnaire; Attachment 3: mRS Assessment Criteria).

f) The mRS assessment will also be performed prior to treatment initiation.

g) Imaging will be performed after the end of the 72-hour continuous infusion (+ 2 days).

h) The neurological assessments will be performed once in the period between the time of consent acquisition and Day 5.

i) The standard 12-lead ECG, vital signs, and clinical laboratory tests (centralized measurements) will be performed before the end of the 72-hour continuous infusion (-1 day).

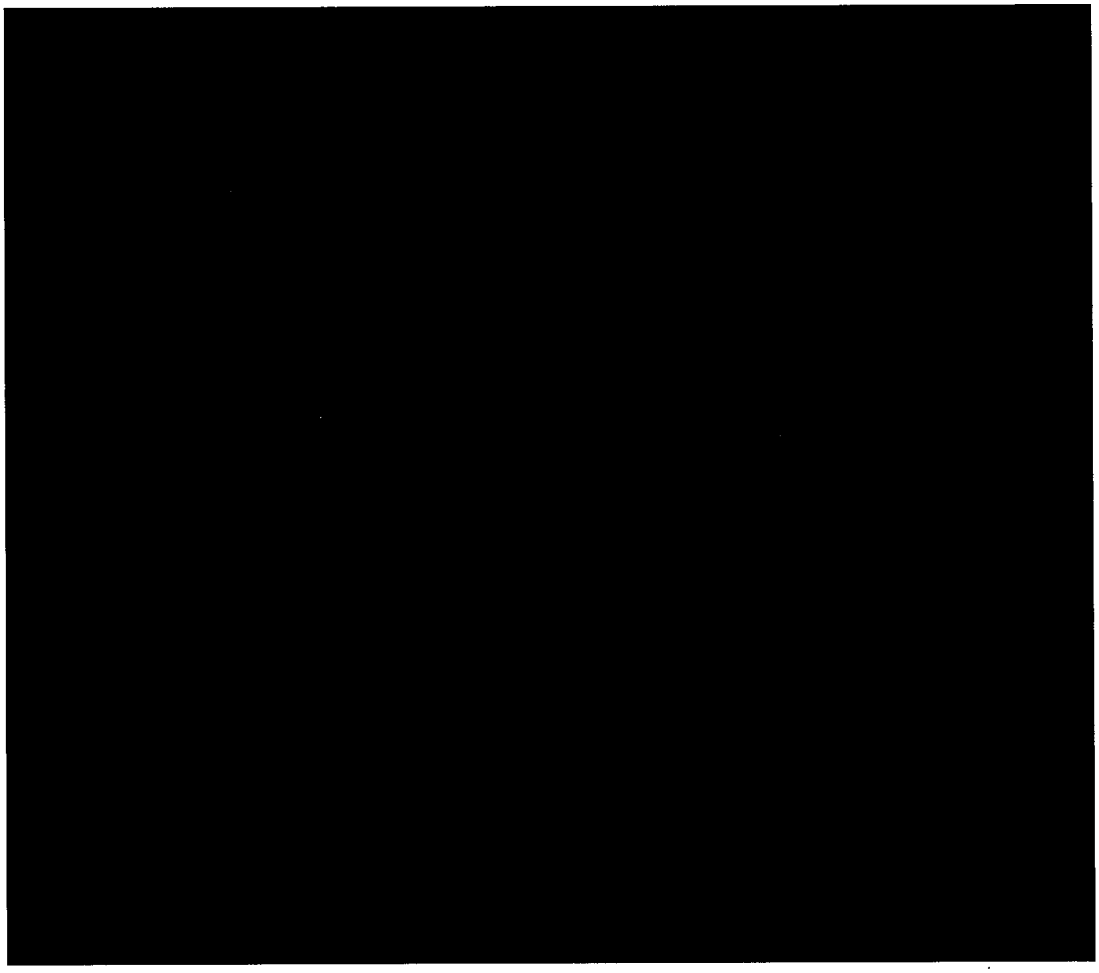
j) The following tests will be conducted urgently at the hospital to confirm the patient's eligibility: WBC, RBC, hematocrit, hemoglobin, platelets, AST (GOT), ALT (GPT), LDH, ALP, γ-GTP, total bilirubin (T-Bil), CK (CPK), urea nitrogen (BUN), serum creatinine (Cre), and eGFR.

k) The red blood cell (RBC), platelet (Plt), AST (GOT), ALT (GPT), LDH, ALP, total bilirubin (T-Bil), CK (CPK), urea nitrogen (BUN), and serum creatinine (Cre) levels only will be performed at the site every day from the day after treatment initiation through Day 5 after treatment initiation to confirm subject safety.

3.3 Sample Size and Power Considerations

- A total of 336 subjects as randomized subjects
  - Group H: 120 subjects
  - Group L: 96 subjects
  - Control group: 120 subjects

Rationale



4. PLANNED ANALYSES

4.1 Data Monitoring Board (DSMB)

No DSMB will be performed for this study.

4.2 Interim Analysis

No interim analysis will be performed for this study.

4.3 Final Analysis

All final, planned analyses identified in this SAP will be performed by MTPC Authorization of this Statistical Analysis Plan, Database Lock, Authorization of Analysis Populations and Unblinding of Treatment.

Final analysis will be done after database lock as per this SAP.

The final database lock will occur when all outstanding data queries have been resolved and the database is fully cleaned. These data will then be used to produce a full set of unblinded tables, figures and listings planned in this SAP for the Clinical Study Report. The tables, figures and listings will then be communicated to the wider study team.

5. ANALYSIS POPULATION(S)

The definitions of the analysis sets are provided below. Efficacy analysis will be performed in the full analysis set (FAS) and safety analysis will be performed in the safety analysis set(SAF).

Full Analysis Set (FAS)	FAS will be defined as all randomized subjects except for the following subjects: - Subjects who were not with cerebral infarction - Subjects to whom the investigational product was not administered at all - Subjects for whom no post-randomization efficacy data are available
Safety Analysis Set (SAF)	The safety analysis population will be defined as all randomized subjects except for the following subjects: - All subjects to whom the investigational product was not administered at all - All subjects for whom no post-randomization safety data are available

The acceptance or rejection of each analysis population will be treated based on the results of the data review meeting on 18 July, M200201 and M203001 are excluded from FAS and SAF.

6. GENERAL CONSIDERATIONS

Efficacy endpoints will be analysed on the FAS population and listed on the FAS population. Subjects will be analysed according to the treatment group they were randomised to. Safety analyses will be performed on the SAF. Subjects will be analysed according to the treatment group they were actually received.

In general, continuous variables will be summarized descriptively using the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the relevant group and population (analysis set) being presented, unless otherwise specified (e.g., on some occasions, percentages maybe calculated out of the total number of subjects with available data at a particular visit and/or time point).

For each section, baseline is the last valid assessment prior to the start of IMP administration. For numerical variables, change from baseline will be calculated as the post-baseline value minus the baseline value. If baseline value cannot be determined for a particular variable, change from baseline will not be calculated.

Data will be handled as follows.

(1) Definition of missing data

When test values are missing, or could not be measured because of, for example, a problem with the test sample, these values will be handled as missing. In addition, no imputation will be made in case of missing values.

(2) Handling of the data at measurement time points

When summarizing the data at each measurement time point, data within the analysis time windows defined in Appendix 1 will be used. If multiple values were obtained within the time window, then the value closest to the planned assessment day will be used.

Unscheduled visits will not be displayed in by-visit summary tables, but will be included in the data listings.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

The date and times of start and end of IMP administration will be taken from the Electronic Case Report Form (eCRF) Dosing form.

All medical history and adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0.

All prior and concomitant medications will be coded using the World Health Organization (WHO) drug dictionary (Version: WHO DDE B2 Mar_2017).

7. STATISTICAL METHODOLOGY

7.1 Study Patients

7.1.1 Disposition of Subjects

Disposition of subjects will be listed.

Number and percent of subjects completed protocol scheduled visits will be presented for each study period (Study drug treatment period and Observation period). Subjects who discontinued in study drug treatment period will be summarized by reasons for discontinuation.

Number and percent of all subjects, and in each protocol defined analysis population will be presented by treatment group and overall wherever applicable.

7.1.2 Demographic and Other Baseline Characteristics

Major demographic and other baseline characteristics will be listed for all subjects.

Table2. Variables related to demographic and other baseline characteristics

Category	Variable	Data format
Subject background	Sex (male, female)	Binary
	Age at consent acquisition (years)	Metric
	Weight (kg)	Metric
	Time from onset to first dose	Metric
	Pre-administration NIHSS Total Score	Metric
	Spasm	Binary
	Race	Category
	Disease type	Category
	Japan Coma Scale	Category
	Medical history	Binary
	Concomitant Medications	Binary
	Concomitant Therapy	Binary
	Person signed Informed Consent	Category

The above demographic and baseline data will be summarized by treatment group. Baseline Weight is taken from the assessments at the Screening visit. Age in years is derived birth date in the eCRF.

Demographic data and other baseline characteristics will be summarised for the SAF by treatment group and overall. The following demographic and other baseline characteristics will be reported for this study: Age, Sex, Weight, Time from onset to first dose, Pre-administration NIHSS Total Score, Spasm, Race, Disease type, Japan Coma Scale, Medical history, Concomitant Medications , Concomitant Therapy, Person signed Informed Consent.

7.1.3 Medical History

All medical history data will be listed.

The frequency and percentage of subjects will be summarised by treatment group and overall for all subjects using Preferred Term nested within System Organ Class (SOC). The summary will be sorted by International Agreed Order (IAO) for SOC and alphabetical order for PT.

If Month and/or Day of medical history start date is missing, January and/or 1 will be used. If Month and/or Day of medical history end date is missing, December and/or 31 will be used.

7.1.4 Concomitant Medications and Concomitant Therapys

All medication/therapy data will be listed.

Concomitant medications/therapys is any medications/therapys that is on-going at the time of the first dose or started after the onset of cerebral infraction. Concomitant medications/thepapys with an incomplete start date but that are still ongoing at the end of the study will be considered as concomitant medications/therapys.

7.1.5 Study Medication Exposure

All exposure data will be listed.

The number of subjects with at least one dose of exposure of IMP will be summarised by treatment group and overall.

The duration of exposure in days will be calculated as:

1) In the case of IMP Exposure for Continuous infusion dosing regimen(hours)

Actual dosing hours =

(Date and time of last bolus dose – Date and time of first bolus dose) +

sum of (Date and time of last div dose – Date and time of first div dose)

2) In the case of IMP Exposure for Approved dosing regimen(days)

Actual dosing days = Date of last dose – Date of first dose +1

If either the date of last dose or the date of first dose cannot be determined then the duration calculation will not be done. The duration of exposure will be summarised by treatment group and overall.

7.1.6 Compliance

All compliance data will be summarised.

The compliance will be calculated as:

1) In the cese of IMP Exposure for Continuous infusion dosing regimen

Actual dosing hours / 72 hours × 100

2) In the case of IMP Exposure for Approved dosing regimen

Actual dosing days / 14 days or 15 days × 100,

where if first dose is evening, then the denominater will be 15 days. Others are 14 days.

7.2 .Efficacy Assessment

7.2.1.1 Adjustment for Covariates

Ajustment for covariates will not be performed.

7.2.1.2 Handling of Dropouts or Missing Data

Unless otherwise specified, data will be used to their maximum possible extent, but without any imputations for missing data, i.e. missing values will not be replaced or estimated.

7.2.1.3 Interim Analyses and Data Monitoring

No interim analysis will be performed for this study and therefore no adjustment on type 1 error will be made.

7.2.1.4 Multicentre Studies

Due to the low number of subjects by centre, a centre effect was not included in any of the statistical analyses.

7.2.1.5 Multiple/Comparisons/Multiplicity

The study is not powered to address multiple statistical comparisons; therefore no adjustment for multiplicity will be made.

7.2.1.6 Use of an 'Efficacy Subset' of Patients

Not applicable in this study.

7.2.1.7 Active-Control Studies Intended to show equivalence

Not applicable in this study.

7.2.1.8 Examinations of Subgroups

Not applicable in this study.

7.2.2 Primary Efficacy Endpoint

NIHSS (change over the 7 days from onset)

NIHSS value and changes from baseline will be summarized descriptively by treatment group and analysis visit.

7.2.3 Secondary Efficacy Endpoints

(1) NIHSS (Day 4, Day 7, Day 10, Day 14, after 3 weeks, at discharge, after 3 months)

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

(3) BI (Day 14, after 3 weeks, at discharge, after 3 months)

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

(5) Start of rehabilitation

(6) Duration of hospitalization

(7) Cranial imaging diagnosis

1) NIHSS

The descriptive statistics will be calculated for the NIHSS scores at Day 4, Day 7, Day 10, Day 14, after 3 weeks, at discharge, and after 3 months. The number and percentage of patients with an improvement of 4 or more points in the NIHSS score will be summarized by treatment group and analysis visit.

2) mRS

The number and percentage of patients with mRS each score (0, 1,…,6) after 3 weeks, at discharge, and after 3 months will be summarized by treatment group.

3) BI

The descriptive statistics for each treatment group will be calculated for the total BI score (0 to 100) at Day 14, after 3 weeks, at discharge, and after 3 months. The number and percentage of patients for BI three categorical score (100-95, 90-55, 50-0) will be summarized by treatment group and analysis visit.

4) FIM

The descriptive statistics for each treatment group will be calculated for the FIM total scores (18 to 126 points) measured after 3 weeks, at discharge, and after 3 months.

The descriptive statistics will also be calculated for the motor item (13 to 91 points) and cognitive item (5 to 35 points) scores.

5) Time of rehabilitation initiation

The descriptive statistics for each treatment group will be calculated for the time of rehabilitation initiation (the start date of rehabilitation minus the start date of hospitalization + 1).

6) Duration of hospitalization

The descriptive statistics for each treatment group will be calculated for the duration of hospitalization (the start date of discharge minus the start date of hospitalization + 1).

(7) Cranial imaging diagnosis

Image analysis

(i) Infarct volume

The descriptive statistics for each treatment group will be calculated for the infarct volume.

(ii) Severity of cerebral edema

The change in the edema will be calculated, and descriptive statistics for each treatment group will be calculated.

(iii) Presence or absence of intracranial bleeding

The proportion of subjects with intracranial bleeding will be calculated by severity, and the descriptive statistics for each treatment group will be calculated.

7.2.4 Other Efficacy

Not applicable in this study.

7.2.5 Quality of Life Assessments

Not applicable in this study.

7.2.6 Exploratory endpoint

[redacted]

7.3 Safety Assessments

7.3.1 Adverse Events

Summaries

All AEs for each subject, including multiple occurrences of the same event, will be presented in full in a comprehensive listing including subject number, treatment, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop date and duration.

AEs which start on or after dosing that are expressed or exacerbated are defined as treatment emergent adverse events (TEAEs).

The frequency and incidence of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT). The summary will be sorted by International Agreed Order (IAO) for SOC and alphabetical order for PT (or by frequency from the highest to the lowest).

Proportion of subjects with any TEAE, subjects with any related TEAE, subjects with any serious TEAE, and subjects with any TEAE leading to discontinuation of the study will be summarized.

Following summaries of TEAEs will be presented:

- Summary of AEs by SOC and PT
- Summary of related AEs by SOC, PT

For summaries of AEs multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a subject will be counted once in the maximum intensity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility>no reasonable possibility). If intensity or relationship is found to be missing the most severe occurrence will be imputed for that particular summary.

7.3.2 Laboratory Tests

Laboratory parameter values and changes from baseline, except for urinalysis will be summarized descriptively by analysis visit.

Clinical significance of laboratory findings will be evaluated by the Investigator with respect to pre-defined clinically relevant ranges taking into account the Investigator site's normal ranges. The laboratory data will be listed in full with clinically relevant values flagged (L=Lower than normal range, H=Higher than normal range or A=Abnormal if no reference range). A listing of laboratory values will be provided for subjects with any clinical significant findings (list relevant laboratory parameters only).

Lab parameter values and changes from baseline will be summarized descriptively by treatment group and analysis visit.

Shift tables will present the changes in clinically relevant categories from baseline to each analysis visit. The categories will be qualitative values for Urinalysis.

The test parameters(from central laboratory) are listed below.

* Hematology tests: White blood cell count (WBC), red blood cell count (RBC), hematocrit (Ht), hemoglobin (Hb), platelets (Plt)
* Blood biochemistry tests: AST (GOT), ALT (GPT), LDH, ALP, γ-GTP, total bilirubin (T-Bil), direct bilirubin (D-Bil), total cholesterol (T-Cho), triglycerides (TG), total protein (TP), CK (CPK), blood urea nitrogen (BUN), serum creatinine (Cre), eGFR, uric acid (UA), Na, K, Cl, albumin, glucose
* Urinalysis (qualitative): Glucose, protein, occult blood

7.3.3 Vital Signs

All vital sign data will be listed.

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, body temperature) values and changes from baseline will be summarized descriptively by analysis visit.

7.3.4 12-lead ECG

All 12-lead ECG (heart rate, RR, PR, QRS, QT, QTcF, overall evaluation) parameters and findings will be listed.

12-lead ECG parameter values and changes from baseline will be summarized descriptively by analysis visit.

For ECGs, number and percentage of subjects meeting the criteria listed below will be presented:

- QTcF > 500 msec at timepoint
- 500≥QTcF >480msec at time point
- 480≥QTcF >450msec at time point
- Change from baseline in QTcF > 30 msec
- Change from baseline in QTcF > 60 msec

Number of normal or abnormal values will be summarized by analysis visit window.

7.3.5 Physical Examinations

Not applicable in the study.

7.3.6 Other Safety Assessments

Neurologic Examination data will be listed.

8. CHANGES FROM THE PROTOCOL

MTPC has decided that this study is prematurely terminated due to reconsideration of the MTPC's product pipeline. Therefore, the stasistical analysis plan is changed form the protocol as follows.

- Per protocol set will be excluded from the analysis populations.
- Efficacy endpoints will be only descriptively summarized without any formal statististical test.

9. REVISION HISTORY FOR SAP AMENDMENTS

Version 02.00 (19 July, 2018)

- It reflects the results of the data review meeting on 18 July 2018.

10. DATA NOT SUMMARISED OR PRESENTED

Not applicable in the study.

11. REFERENCES

[redacted]

12. VALIDATIONS

All statistical analyses will be performed using SAS version 9.3 or higher. The quality of statistical results will be ensured by double programming at Takumi Information Technology Inc.,.

13. PROGRAMMING AND DATA PRESENTATION CONVENTIONS

The following sections detail all listings, tables, figures that will be produced in conjunction with the report.

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Listings, Tables and Graphs
Continuous infusion high-dose group	L group
Continuous infusion low-dose group	H group
Approved dosing regimen group	Control Group

(1) Only shown where appropriate.

Listings will be presented in treatment, subject, visit (where applicable) and date (where applicable) order. Listings will be produced (landscape in MS Word) using PROC REPORT in SAS monospace font and pitch 8.

Summary tabulations will be presented by treatment group (and overall if appropriate), scheduled visit order (if appropriate). Continuous data summaries will present (unless stated otherwise) number of observations, number of missing observations (if there are any), mean, standard deviation, median, minimum and maximum. Categorical data summaries will present the number of observations and the corresponding percentage.

Number of decimal places (DP) or significant digits (SD):

Describe here the requirements, preferably in a table format, see example below:

Statistic	Specification	Apply to
Minimum, maximum	same number of DPs as the data provided in the datasets	All original, i.e. non-derived, data provided in the datasets
mean, median, SD, confidence intervals	one more DP than the raw data	All
Percentages	1 DP	All
p-values	3 DP	All

Example guidelines for presentation of data

- Column headers in mixed case, with "(N=nn)" below treatments to denote the denominator
- decimal places aligned
- N (%) as a separate column rather than included in brackets for each element of the table,
- Categories (i.e. in column 1) in sentence case, in the order on the CRF
- Ordering of statistics N, Missing, Mean, SD, Minimum, Median and Maximum (and labelled as such). CV%, geometric means and 95% CIs for geometric mean also for PK parameters.
- Tables will be produced in landscape in MS Word using PROC REPORT in SAS monospace font and pitch 8.

14. LIST OF LISTINGS, TABLES AND FIGURES

The tables, figures and listings listed in this section are the minimum requirement. A complete list should be included in the SAP.

14.1 Listings

No.	Title of listing	Analysis Population/Dataset
	16.2.1 – SUBJECT DISPOSITION	
16.2.1.1	Randomisation details	All Subjects
16.2.1.2	Subject Dispositions	All Subjects
	16.2.2 – ANALYSIS POPULATIONS	
16.2.2.1	Analysis Population	All Subjects
	16.2.3 – DEMOGRAPHY AND BASELINE CHARACTERISTICS	
16.2.3.1	Demography or Baseline Characteristics	All Subjects
16.2.3.2	Medical History	All Subjects
16.2.3.3	Concomitant Medications	All Subjects
16.2.3.4	Concomitant Therapys	All Subjects
	16.2.4 – EXPOSURE AND COMPLIANCE	
16.2.4.1	IMP Exposure for Continuous Infusion Dosing Regimen	All Subjects
16.2.4.2	IMP Exposure for Approvel Dosing Regimen	All Subjects
	16.2.5 – EFFICACY	
16.2.5.1	NIHSS	FAS
16.2.5.2	mRS	FAS
16.2.5.3	BI	FAS
16.2.5.4	FIM	FAS
16.2.5.5	Head Image Diagnosis	FAS
	16.2.6 – ADVERSE EVENTS	
16.2.6.1	Adverse Events	SAF
	16.2.7 – OTHER SAFETY ASSESSMENTS	
16.2.7.1	Neurological Examination	SAF
16.2.7.2	12-lead ECG	SAF
	16.2.8 – [redacted]	
16.2.8.1	[redacted]	All Subjects

14.2 Tables

No.	Title of table	Analysis Population/Dataset
	14.1 – STUDY	
14.1.1.1	Analysis Populations	All Subjects
14.1.1.2	Subject Dispositions	All Subjects
14.1.2.1	Baseline Demographics	All Subjects
14.1.2.2	Medical History	All subjects
14.1.2.3	Summary of IMP Exposure for Continuous Infusion Dosing Regimen	All subjects
14.1.2.4	Summary of IMP Exposure for Approved dosing regimen	All subjects
	14.2 – EFFICACY	
14.2.1.1	Summary of NIHSS (Change from Pre-NIHSS Score ≧ 4)	FAS
14.2.1.2	Summary of NIHSS	FAS
14.2.1.3	Summary of mRS	FAS
14.2.1.4	Summary of BI	FAS
14.2.1.5	Summary of BI(100-95, 90-55, 50)	FAS
14.2.1.6	Summary of FIM	FAS
14.2.1.7	Summary of FIM(moter item, cognitive item)	FAS
14.2.1.8	Summary of Duration of hospatalization	FAS
14.2.1.9	Summary of Start of rehabilitation	FAS
	14.3 – SAFETY	
14.3.1.1	Overall Summary of Treatment Emergent Adverse Events	SAF
14.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	SAF
14.3.1.3	Summary of Adverse Drug Reaction by System Organ Class and Preferred Term	SAF
14.3.2.1	Summary of Hematolog	SAF
14.3.2.2	Summary of Biochemical	SAF
14.3.2.3	Summary of Urianalysis	SAF
14.3.2.4	Shift Table for Hematology	SAF
14.3.2.5	Shift Table for Biochemical	SAF
14.3.2.6	Shift Table for Urianalysis	SAF
14.3.3.1	Summary of Vital Signs	SAF
14.3.4.1	Summary of 12 lead ECG parameters	SAF
14.3.4.2	Number of Subject Meeting QTcF Criteria in 12-lead ECG	SAF
14.3.4.3	Summary of 12-lead ECG - Number of Normal/Abnomal values	SAF
	14.4 – [redacted]	
14.4.1.1	Summaey of [redacted]	All subjects

15. APPENDIX 1 – ANALYSIS TIME WINDOW

Data handling (Safety and Efficacy assessment)

The acceptable windows of the visit of evaluations and measurements are as follows:

Period	Visit	Targeted Study Days*	Analysis Visit	Analysis Visit Window in Study Days
Befor Treatment Initiation	Confirmation of suitability	0	Baseline	[0, 1 (Day 1 prior to treatment initiaion)] **
Study Drug Treatment Period	Day 1	1	Day 1	1 (Day 1 after treatment initiation)
	Day 2	2	Day 2	2
	Day 3	3	Day 3	3
	Day 4	4	Day 4	4 or [3, 4]*** or [4, 6]***
	Day 5	5	Day 5	5
	Day 7	7	Day 7	[6, 8]
	Day 10	10	Day 10	[9, 11]
	Day 14	14	Day 14	[14, 15]
	Study drug treatment period discontinuation	-	Study drug treatment period discontinuation	[Study drug treatment period discontinuation day, Study drug treatment period discontinuation day + 1]
Observation period	After 3 weeks	22	After 3 weeks	[20, 24]
	At discharge	-	At discharge	[At discharge day - 1, At discharge day]
	After 3 months or at observation period discontinuation	85	After 3 months	[77, 93]
	At observation period discontinuation	-	At observation period discontinuation	[At observation period discontinuation day, At observation period discontinuation day +8]

* Study days will be calculated from the first dose of study drug.

** The neurological assessments at baseline will be performed once in the period from the time of consent acquisition to Day 5.

*** Labolatory tests, Vital signs and 12-Lead ECG will be measured before continuous intravenous injection of 72 hours (-1 day) and Head Image Diagnosis will be taken after continuous intravenous injection of 72 hours (2 days).