STATISTICAL ANALYSIS PLAN

Protocol No.	MCI-186-J22
Protocol Title	An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Mild or Moderate Renal Impairment Compared to Subjects with Normal Renal Function
Version History	Version 1.0 First approved version / 9 May, 2018 Version 2.0 Final approved version / 20 June, 2018
Author	[redacted]

APPROVAL FORM

The approval signatories below have reviewed this Statistical Analysis Plan (SAP) and agreed on the planned analyses defined in this document.

[redacted]

Name: Date: Signature:

[redacted]

Position:

[redacted]

MTPC Statistics Approver [redacted]

Name: Date: Signature:

[redacted]

Position:

[redacted]

MTPC Pharmacokinetics Approver [redacted]

Name: Date: Signature:

[redacted]

Position:

[redacted]

MTPC Statistics Reviewer [redacted]

Name: Date: Signature:

[redacted]

Position:

[redacted]

MTPC Pharmacokinetics Reviewer [redacted]

Name: Date: Signature:

[redacted]

Position:

[redacted]

MTPC Statistics Reviewer [redacted]

Name: Date: Signature:

[redacted]

Position:

[redacted]

MTPC Pharmacokinetics Reviewer [redacted]

Name: Date: Signature:

[redacted]

Position:

[redacted]

TABLE OF CONTENTS

1. INTRODUCTION 8
1.1 Study Design 8
1.2 Schedule of Study Procedures 8
2. STUDY OBJECTIVE(S) AND ENDPOINTS 10
2.1 Study Objective(s) 10
2.1.1 Primary objective(s) 10
2.1.2 Secondary objectives 10
2.2 Pharmacokinetics Endpoint(s)/Evaluation(s) 10
2.2.1 Primary endpoint(s) 10
2.2.2 Secondary endpoints 10
2.2.3 Exploratory endpoints 11
2.3 Safety Assessment(s) 11
3. PLANNED ANALYSES 11
4. ANALYSIS POPULATION(S) 11
5. GENERAL CONSIDERATIONS 12
5.1 Subjects Composition 12
5.2 Analysis Time Window for Visits 12
5.3 Number of Digits to Report 13
5.4 Significance level and confidence level 14
5.5 Descriptive statistics values to calculate 14
5.6 Derived variables 14
6. SAMPLE SIZE AND POWER CONSIDERATIONS 15
7. STATISTICAL METHODOLOGY 15
7.1 Disposition of Subjects 15
7.2 Demographic and Other Baseline Characteristics 15
7.3 Medical History 15

7.4 Prior and Concomitant Medications 16
7.5 Study Drug Exposure 16
7.6 Treatment Compliance 16
7.7 Statistical/Analytical issues 16
7.7.1 Adjustments of covariates 16
7.7.2 Handling of Dropouts or Missing Data 16
7.7.3 Interim Analyses and Data Monitoring 16
7.7.4 Multicentre Studies 16
7.7.5 Multiple Comparison/Multiplicity 16
7.7.6 Use of an "Efficacy Subset" of Patients 16
7.7.7 Active-Control Studies Intended to Show Equivalence 17
7.7.8 Examination of Subgroups 17
7.7.9 Handling of Laboratory Test Values 17
7.8 Pharmacokinetic Assessments 17
7.8.1 Analysis of Individual Plasma Concentrations 17
7.8.2 Analysis of Pharmacokinetic Parameters 18
7.9 Safety Assessments 18
7.9.1 Adverse Events 19
7.9.2 Laboratory Tests 19
7.9.3 Vital Signs 20
7.9.4 12-lead ECG 20
7.9.5 Physical Examinations 20
7.9.6 Withdrawals 20
7.9.7 Other Safety Assessments 20
8. CHANGES FROM THE PROTOCOL 20
9. DATA NOT SUMMARISED OR PRESENTED 20
10. REFERENCES 21

11. VALIDATIONS 21

12. LISTINGS, TABLES AND FIGURES 21

12.1 Listings 21

12.2 Tables 22

12.3 Figures 22

13. REVISION HISTORY FOR SAP AMENDMENTS 23

APPENDIX 1 – PHARMACOKINETIC PARAMETER CALCULATIONS 24

Abbreviations

AE	:	adverse event
ANOVA	:	analysis of variance
BLQ	:	below limit of quantification
BMI	:	body mass index
CI	:	confidence interval
CV	:	coefficient of variation
DBL	:	database lock
DP	:	decimal places
ECG	:	electrocardiogram
eCLcr	:	estimated creatinine clearance
eGFR	:	estimated glomerular filtration rate
IAO	:	International Agreed Order
IMP	:	investigational medicinal product
LLOQ	:	lower limit of quantification
LSmeans	:	least squares means
MedDRA	:	Medical Dictionary for Regulatory Activities
PK	:	pharmacokinetics
PT	:	preferred term
QC	:	quality control
ρ	:	Spearman's rank correlation coefficient
SAP	:	statistical analysis plan
SAE	:	serious adverse event
SD	:	standard deviation
SOC	:	system organ class
TEAE	:	treatment emergent adverse event
WHO-DD	:	World Health Organization Drug Dictionary

List of PK Parameters		
Parameters	**Unit**	**Definitions**
$AUC_{0\text{-last}}$	h•ng/mL	Area under the plasma concentration-time curve from zero up to the last quantifiable concentration time point
$AUC_{0\text{-}\infty}$	h•ng/mL	Area under the plasma concentration-time curve from zero up to infinity with extrapolation of the terminal phase
[redacted]		
C_{max}	ng/mL	Maximum plasma concentration after administration
[redacted]		
$t_{1/2}$	h	Terminal elimination half-life in plasma concentration-time course
[redacted]		

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol dated 02 April 2018. The plan covers statistical analysis plan, tabulations and listings of pharmacokinetic (PK) and safety data to assess the pharmacokinetics and safety of MCI-186 after a single intravenous infusion of 30 mg over 60 min in subjects with mild or moderate renal impairment compared to subjects with normal renal function.

The SAP is prepared by [redacted] The statistical analyses and production of the outputs described in the SAP will be conducted and QC checked by [redacted] Data Science Department, using SAS® 9.3 or a later version. The final analyses and outputs will be approved by Mitsubishi Tanabe Pharma Corporation.

1.1 Study Design

This is open label, single dose study in male and female subjects with mild or moderate renal impairment, and normal renal function.

The study will be conducted in the following three groups.

Group 1: Subjects with mild renal impairment eGFR 60-89 mL/min/1.73m^2 as determined by the 3-variable Japanese equation

Group 2: Subjects with moderate renal impairment (eGFR 30-59 mL/min/1.73m^2)

Group 3: Subjects with healthy normal renal function to match Group 1 and Group 2 for age, body weight, and gender (eGFR≥90 mL/min/1.73m^2)

1.2 Schedule of Study Procedures

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

Table 1 Time and events schedule

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

2. STUDY OBJECTIVE(S) AND ENDPOINTS

2.1 Study Objective(s)

2.1.1 Primary objective(s)

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

2.1.2 Secondary objectives

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

2.2 Pharmacokinetics Endpoint(s)/Evaluation(s)

The Pharmacokinetics parameters of MCI-186 unchanged and the sulfate conjugate will be calculated by Non-compartmental analysis using [redacted] or a later version Software. The time used to calculate the pharmacokinetic parameters will be the actual time (rounded to two decimal places) with the time of the investigational drug administration taken as 0.00 hours. When the same parameter has Observed and Predicted values, Observed value will be adopted. In addition, the concentration below the quantitation limit (BLQ) will be considered as a numerical value of 0 and calculation will be performed.

2.2.1 Primary endpoint(s)

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

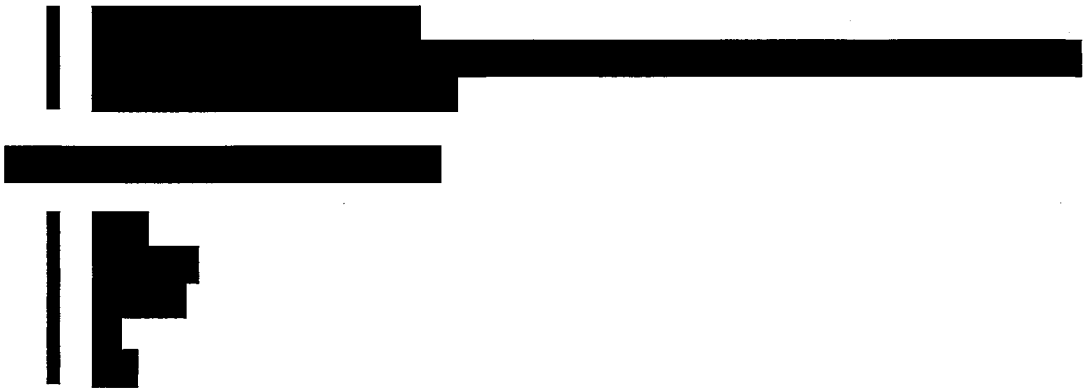
- Peak drug concentration (C_{max});
- Area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}last}$);
- Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}\infty}$).

2.2.2 Secondary endpoints

The following secondary endpoints will be evaluated during the study:

PK parameters of MCI-186

- Half-life ($t_{½}$);
- [redacted]



2.2.3 Exploratory endpoints

Not applicable in the study.

2.3 Safety Assessment(s)

The following secondary endpoints will be evaluated the study:

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 ECG parameters;
- Laboratory assessments including haematology, biochemistry, coagulation and urinalysis.

3. PLANNED ANALYSES

The pharmacokinetics of MCI-186 and its metabolite after a single intravenous infusion of 30 mg over 60 min will be evaluated in subjects with mild or moderate renal impairment compared to subjects with normal renal function.

The statistical analyses will be performed after database lock(DBL). Interim analysis will not be carried out.

4. ANALYSIS POPULATION(S)

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

Safety analysis set:	All subjects who have received at least one dose of investigational medicinal product (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.

The acceptance or rejection of each analysis population will be treated based on the results of the data review meeting on 29 May, 2018 as follows.

Safety analysis set:	No subject is excluded from analysis.
PK analysis set:	It was agreed that 8 subjects (J220104, J220108, J220109, J220127, J220135, J220143, J220144, J220145) are excluded from PK analysis.

For cases that subjects were not adopted in the PK analysis set, all PK data will be rejected and no parameters will be calculated. Furthermore, for cases that subjects adopted in the PK analysis set and partial data not being adopted, PK parameters will be calculated from only the adopted data.

After study completing for all renal impairment subjects (Group 1 and Group 2), a blind data review for created PK analysis set of the renal impairment population will be held to enrol matched healthy subjects for Group 3 with respect to age, gender and body weight.

Also, after study completing for all subjects, a data review meeting will be held to decide data handling rules. SAP ver.1.0 will be fixed before a data review meeting.

5. GENERAL CONSIDERATIONS

5.1 Subjects Composition

Male or female subjects with mild renal impairment (Group 1, n=11), moderate renal impairment (Group 2, n=8) and normal renal function (Group 3, n=11) as defined using the estimation of glomerular filtration rate (eGFR) based on the 3-variable Japanese equation at Day -1.

- Group 1: Subjects with mild renal impairment (eGFR 60-89 mL/min/1.73m^2 as determined by the 3-variable Japanese equation)
- Group 2: Subjects with moderate renal impairment (eGFR 30-59 mL/min/1.73m^2)
- Group 3: Subjects with healthy normal renal function to match Group 1 and Group 2 for age, body weight, and gender (eGFR≥90 mL/min/1.73m^2)

5.2 Analysis Time Window for Visits

Analysis time windows for blood sampling for PK measurements are as follows.

[redacted]

Analysis time windows for safety evaluation are as follows.

Screening (Day -21 to Day -2)	Not specified
Hospitalization (Day -1)	Not specified
Before dosing (Day 1)	Before dosing time
24 h and 48 h after dosing (Day 2 and Day 3)	Scheduled time ± 1 hour (except for urinalysis)
	Until scheduled time + 1 hour (urinalysis)
Follow-up (Day 7 + 2days)	Not specified

5.3 Number of Digits to Report

Statistical analysis variables, statistics to be calculated and number of digits to report are as follows.

Laboratory tests Physical examinations Standard 12-Lead ECG	Mean, SD, median	Report to one extra digit plus the determined/specified digits
	Minimum, maximum	Report to the determined/specified digits
Pharmacokinetics	Mean, SD, minimum, median, maximum, geometric mean, geometric LSmeans, CI	Report to the determined/specified digits
	Ratio of geometric LSmeans	Up to 3 decimals
	Degree of freedom	Integer
	Sum of squares, Mean square	Up to 4 decimals
	α, β, ρ	4 significant digits
	F-value	Up to 2 decimals the following also applies: if F-value<0.01, displayed "F<0.01".
	p-value	Up to 4 decimals the following also applies: if p-value<0.0001, displayed "p<0.0001".
General information	Number of subjects, number of valid observations, number of events, number of cases	Integer
	CV%, geometric CV%, Percentages (%)	To the first decimal place (DP)

5.4 Significance level and confidence level

The significance level of the statistical test will be 5% (two-sides). The two-sided confidence level of the confidence interval will be 95%. The two-sided confidence level for comparison between groups will be 90%.

5.5 Descriptive statistics values to calculate

Where appropriate, continuous variables will be summarized descriptively, using the number of observations, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

5.6 Derived variables

(1) Definition(s) of baseline(s)

The baseline of vital signs and 12-lead ECG is the final evaluable value obtained before IMP administration on Day 1.

The baseline of clinical laboratory values will be the value obtained on Day -1.

(2) Age at informed consent

Age (years) = Year of informed consent - Year of birth

Subtract 1 from the age (years) calculated above, if [Month of informed consent < Month of birth] or [Month of informed consent = Month of birth AND Day of informed consent < Day of birth].

(3) BMI

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

Height will be the value obtained at screening.

The value will be rounded off at the second decimal place and reported to the first decimal place.

(4) Adverse events

The MedDRA/J version 20.0 will be used as a unified dictionary in the assessment of AEs.

(5) Adverse reactions

Adverse reactions are defined as AEs that are determined to have a "Reasonable Possibility" of causal relationship to the IMP.

6. SAMPLE SIZE AND POWER CONSIDERATIONS

The planned sample size of six evaluable subjects per renal impairment subjects group and per healthy subjects group is not based on a power calculation, but is determined based on experience to be adequate to obtain reliable results, which meets the objectives of this study.

7. STATISTICAL METHODOLOGY

7.1 Disposition of Subjects

Disposition of subjects will be listed.

- Number and percent of subjects completed protocol scheduled visits will be presented.
- Subjects' status for each study period/phase will be summarized wherever applicable. Subjects who discontinued in each period/phase will be summarized by reasons for discontinuation.

7.2 Demographic and Other Baseline Characteristics

Major demographic and other baseline characteristics will be listed.

For each analysis set, major demographic and other baseline characteristics will be summarized. For countable values, frequency and percentage will be reported. For metric values, descriptive statistics values (number of subjects, mean, SD, minimum, median, and maximum) will be calculated.

Table. Variables related to demographic and other baseline characteristics

Category	Variable	Data format
Subject background	Sex (male, female)	Binary
	Age at consent acquisition (years)	Metric
	Height (cm)	Metric
	Weight (kg) on Day -1	Metric
	BMI on Day -1	Metric
	eGFR on Day -1	Metric
	eCLcr on Day -1	Metric
	Smoking habits	Binary
	Alcohol consumption habits	Binary
	Medical history	Binary
	Complications	Binary

7.3 Medical History

All medical history data will be listed.

7.4 Prior and Concomitant Medications

All medication data will be listed.

All medication data will be coded according to the latest version of WHO-DD and Anatomical Therapeutic Chemistry (ATC) classification, and will be summarized by each group (Groups 1, 2 and 3). Incidence tables will be summarized with ATC Level 2 code, text and Drug Code, Drug Name.

7.5 Study Drug Exposure

All exposure data will be listed.

7.6 Treatment Compliance

All compliance data will be listed.

7.7 Statistical/Analytical issues

7.7.1 Adjustments of covariates

Adjustments of covariates will not be performed.

7.7.2 Handling of Dropouts or Missing Data

Missing data, such as rejected values, will not be imputed.

7.7.3 Interim Analyses and Data Monitoring

Not applicable in the study.

7.7.4 Multicentre Studies

Not applicable in the study.

7.7.5 Multiple Comparison/Multiplicity

Adjustments of multiplicity will not be performed.

7.7.6 Use of an "Efficacy Subset" of Patients

Not applicable in the study.

7.7.7 Active-Control Studies Intended to Show Equivalence

Not applicable in the study.

7.7.8 Examination of Subgroups

Not applicable in the study.

7.7.9 Handling of Laboratory Test Values

In the case of clinical laboratory test values including equality and inequality sign, exclude equality and inequality sign and use for summarized.

7.8 Pharmacokinetic Assessments

7.8.1 Analysis of Individual Plasma Concentrations

All measured plasma concentrations will be listed.

Plasma concentrations will be summarized at each scheduled sampling time point by each group (Groups 1, 2 and 3). The following descriptive statistics will be calculated: N (number of subjects), n (number of valid observations), arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%. Nominal sampling times will be displayed in the summary. For the calculation of the descriptive statistics other than geometric mean and geometric CV%, concentration values reported as BLQ will be set to 0. For the calculation of the geometric mean and geometric CV%, concentration values reported as BLQ will be set to ½ of LLOQ.

CV% and Geometric CV% will be calculated as follows:

$$\text{CV\%} = \frac{\text{SD}}{\text{arithmetic mean}} \times 100$$

$$\text{Geometric CV\%} = [\exp(\sigma^2) - 1]^{1/2} \times 100$$

where σ represents the SD computed on the natural logarithmic transformed concentrations.

To visualize the concentration-time profiles of each group, the following plots will be produced in linear and semi-logarithmic scales:

1. Individual subject concentration-time plot for each group (Groups 1, 2 and 3) overlaid in one graph.
2. Mean concentration-time plot for each group (Groups 1, 2 and 3) overlaid in one graph.

In the summary tables, arithmetic mean, SD, minimum, median, maximum and geometric mean will be presented with the number of significant digits which individual concentrations are reported. In addition, CV%, and geometric CV% will be presented with 1 decimal place.

7.8.2 Analysis of Pharmacokinetic Parameters

All PK parameters will be listed.

The PK parameters will be summarized by each group (Groups 1, 2 and 3). The following descriptive statistics will be calculated: N (number of subjects), n (number of valid observations), arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%.

For the descriptive statistics, the minimum and maximum will be presented according to following requirement:

[redacted]

- C_{max}: will be presented with the number of significant digits they are reported with.

[redacted]

- Other PK parameters: will be presented with a fixed number of decimal places for each parameter. The number of decimal places is 2 decimal places corresponding to having 3 significant digits at the minimum by analyte.

Mean, SD, median and geometric mean will be presented with the number of decimals as follows.

- C_{max}: will be presented with 4 significant digits.
- Other PK parameters: will be presented with 2 decimal places.

CV% and geometric CV% will be presented with 1 decimal place.

To visualize the relationship between measures of renal function and between the PK parameters of MCI-186 and the sulfate conjugate, the following scatter plots of $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, [redacted] and C_{max} (on the verticalaxis) versus eGFR and eCLcr (on the horizontal axis) with regression line, will be produced in linear scales:

1. The PK parameters of ($AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, [redacted] and C_{max} of MCI-186 and the sulfate conjugate) vs (eGFR and eCLcr) plot will be produced for all subjects overlaid in one graph.

Regarding the log-transformed values of $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} of MCI-186 and the sulfate conjugate, analysis of variance (ANOVA) will be performed with groups as factors.

The estimated LSmeans and associated two-sides 95% confidence intervals for these PK parameters in each group, and the estimated LSmeans and associated two-sided 90% confidence intervals for the differences of each the renal impairment group (Group 1 or 2) compared to the normal renal function group (Group 3) will be calculated.

The calculated values will be retransformed using antilogarithms and displayed.

7.9 Safety Assessments

No imputation will be made in case of missing values.

7.9.1 Adverse Events

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. Deaths that occur during the study will be listed.

Duration of the AE and time to the AE occurrence from start of the IMP will be calculated and presented in days (duration = AE stop date – AE start date + 1).

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).

Following summaries of TEAEs will be presented:

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

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.

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

7.9.2 Laboratory Tests

All laboratory parameter will be listed.

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

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 each group (Groups 1, 2 and 3) and analysis visit window.

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

7.9.3 Vital Signs

All vital sign data will be listed.

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

7.9.4 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 window.

7.9.5 Physical Examinations

All physical examinations data will be listed.

7.9.6 Withdrawals

All subjects who are withdrawn from the study will be listed, and its discontinuation assessment will be excluded from summarized.

7.9.7 Other Safety Assessments

Not applicable in the study.

8. CHANGES FROM THE PROTOCOL

Not applicable in the study.

9. DATA NOT SUMMARISED OR PRESENTED

Not applicable in the study.

10. REFERENCES

1. Imai E, Yasuda Y, Makino H. Japan association of chronic kidney disease initiatives (J-CKDI). JMAJ. 2011; 54: 403-405.

11. VALIDATIONS

SAS® for Windows (release 9.3 or a later version) will be used for statistical analyses.

[redacted] will be used to calculate Pharmacokinetics Parameters.

The quality of statistical results will be ensured by double programming at ICRO.

12. LISTINGS, TABLES AND FIGURES

12.1 Listings

No.	Title of listing	Analysis Population/Dataset
16.2.1 – Subject Disposition		
	Subject Dispositions	All Subjects
	Withdrawals	All Subjects
16.2.2 – Inclusion and Exclusion Criteria		
	Inclusion and Exclusion Criteria	All Subjects
16.2.3 – Demography and Baseline Characteristics		
	Demography and Baseline Characteristics	All Subjects
16.2.4 – Medical History and medications		
	Medical history and Complications	All Subjects
	Prior and Concomitant Medications	All Subjects
16.2.5 – Exposure and Compliance		
	Study Drug Exposure and Compliance	All Subjects
16.2.6 – Pharmacokinetics		
	List of Blood Collection Time for Pharmacokinetic Evaluation	All Subjects
	List of Plasma Concentrations	All Subjects
	List of Plasma Pharmacokinetic Parameters	All Subjects
16.2.7 – Adverse Events		
	Adverse Events	All Subjects
16.2.8 – Laboratory Parameters		
	Laboratory Tests - Haematology	All Subjects
	Laboratory Tests - Biochemistry	All Subjects
	Laboratory Tests - Coagulation	All Subjects
	Laboratory Tests - Urinalysis	All Subjects
16.2.9 – Other safety assessments		
	Physical Examinations, Weight and BMI	All Subjects
	Vital Signs	All Subjects
	12-Lead ECG	All Subjects

12.2 Tables

No.	Title of table	Analysis Population/Dataset
14.1 – Study		
	Subjects Dispositions and Analysis Population	All Subjects
	Demography and Baseline Characteristics	Safety, PK
	Summary of Prior Medications	Safety
	Summary of Concomitant Medications	Safety
14.2 – Pharmacokinetics		
	Descriptive Statistics for Plasma Concentrations	PK
	Descriptive Statistics for Plasma Pharmacokinetic Parameters	PK
	Estimate of the Ratio of Geometric LSmeans for pharmacokinetic parameters of each renal impairment group (Groups 1 and 2) with relative to the normal renal function group (Group 3)	PK
14.3 – Safety		
	Summary of Treatment Emergent Adverse Events	Safety
	Incidence and Frequency of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety
	Incidence and Frequency of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Safety
	Incidence and Frequency of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relation to Study Drug	Safety
	Summary of Laboratory Tests - Haematology	Safety
	Summary of Laboratory Tests - Biochemistry	Safety
	Summary of Laboratory Tests - Coagulation	Safety
	Summary of Laboratory Tests - Urinalysis	Safety
	Summary of Laboratory Tests – Clinical Assessment	Safety
	Shift table of Laboratory Tests - Urinalysis	Safety
	Weight	Safety
	Vital Signs	Safety
	Vital Signs - overall evaluation	Safety
	12-Lead ECG	Safety
	12-Lead ECG - overall evaluation	Safety

12.3 Figures

No.	Title of figure	Analysis Population/Dataset
14.2 – Pharmacokinetics		
	Profile of Mean Plasma Concentrations	PK
	Scatter plots of the PK parameters of ($AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, [redacted] and C_{max} of MCI-186 and the sulfate conjugate) vs (eGFR and eCLcr) plot for all subjects overlaid in one graph	PK

No.	Title of figure	Analysis Population/Dataset
16.2.6 – Pharmacokinetics		
	Profile of Individual Plasma Concentrations	PK

13. REVISION HISTORY FOR SAP AMENDMENTS

Version 2.0 (20 June, 2018)

It reflects the results of the data review meeting on 29 May, 2018.

In list of abbreviations and Section 5.3, Pearson's r deleted and Spearman's ρ added.

In Section 1, as protocol changes, the applicable protocol version number has been changed.

In Section 7.8.2, the axis type of the scatterplot has been changed from logarithmic axis to linear axis.

In Section 12.1, "All Subjects" were specified in all parts of the "Analysis Population/Dataset" column.

APPENDIX 1 – PHARMACOKINETIC PARAMETER CALCULATIONS

- Actual blood sampling times for the assay of MCI-186 will be used in the calculation of pharmacokinetic parameters
- All concentrations below the LLOQ will be set at zero for pharmacokinetic calculations
- When [redacted] is missing (or cannot be determined), [redacted] points will not be calculated

PK Parameter Calculations		
Parameters	Unit	Calculation
$AUC_{0\text{-last}}$	h•ng/mL	will be calculated using the linear trapezoidal method and actual times $AUC_{0-last} = \sum_{i=1}^{n} \frac{t_i - t_{i-1}}{2}(C_{i-1} + C_i)$
$AUC_{0\text{-}\infty}$	h•ng/mL	$AUC_{0-\infty} = AUC_{0-last} + \frac{C_{last}}{\lambda_z}$
[redacted]		
C_{max}	ng/mL	will be determined using maximum drug concentration
[redacted]		

PK Parameter Calculations		
Parameters	Unit	Calculation
[redacted]		
$t_{1/2}$	h	$t_{½}$ will be determined as: $$t_{1/2} = \frac{\log_e(2)}{\lambda_z}$$
[redacted]		