STATISTICAL ANALYSIS PLAN

Protocol No.	MCI-186-J23
Protocol Title	A Multi-Center, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MCI-186 in Subjects with Mild or Moderate Hepatic Impairment Compared to Subjects with Normal Hepatic Function
NCT Number	NCT03289234
Version History	Version 1.0 First approved version / 20 September 2018 Version 2.0 Final approved version / 9 October 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.

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Abbreviations

AE	:	adverse event
ANOVA	:	analysis of variance
α	:	intercept of regression line
β	:	slope of regression line
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 2 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 hepatic impairment compared to subjects with normal hepatic 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 multi-center open label, single dose study in male and female subjects with mild or moderate hepatic impairment, and normal hepatic function.

The study will be conducted in the following three groups.

Group 1: Subjects with mild hepatic impairment (Child-Pugh total score of 5 or 6)

Group 2: Subjects with moderate hepatic impairment (Child-Pugh total score of 7 to 9)

Group 3: Subjects with healthy normal hepatic function to match Group 1 and Group 2 for age, body weight, and gender

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	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 hepatic impairment compared to subjects with normal hepatic function.

2.1.2 Secondary objectives

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

2.2 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:

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

- Half-life ($t_{½}$);

[redacted]

2.2.3 Exploratory endpoints

Not applicable in the study.

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 hepatic impairment compared to subjects with normal hepatic 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.

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 hepatic impairment subjects (Group 1 and Group 2), a blind data review for created PK analysis set of the hepatic 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.

The acceptance or rejection of each analysis population will be treated based on the results of the data review meeting on 25 September, 2018 as follows.

Safety analysis set: No subject is excluded from analysis.

PK analysis set: No subject is excluded from analysis.

5. GENERAL CONSIDERATIONS

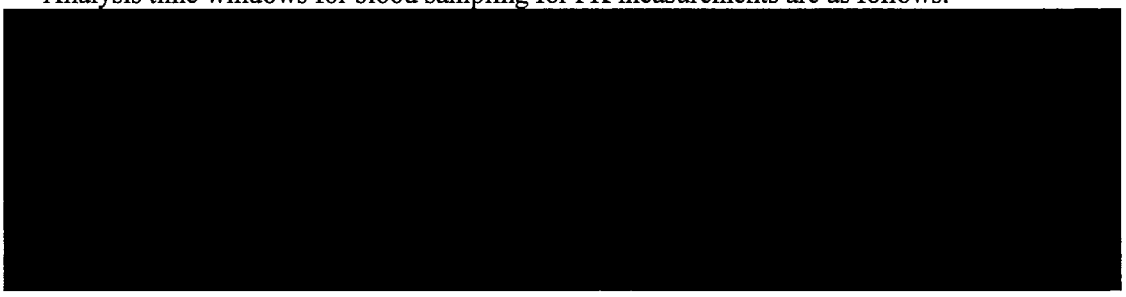
5.1 Subjects Composition

Male or female subjects with mild hepatic impairment (Group 1, n=8), moderate hepatic impairment (Group 2, n=8) and normal hepatic function (Group 3, n=8) as defined using the Child-Pugh classification (subjects with hepatic impairment only).

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

5.2 Analysis Time Window for Visits

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



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 Handling of data for pharmacokinetic assessments

The allowable ranges for the collection of blood samples for the measurement of the serum drug concentrations are shown in Section 5.2. Only valid PK data will be included in the summary tables or figures. PK data that are considered "invalid" or "abnormal" will be flagged in the listing. The PK data handling will be confirmed during blinded data review. Also, PK analysis excluding these possible outliers will be conducted for secondary/sensitivity analysis.

5.4 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	To the 3 decimal places
	Degree of freedom	Integer
	Sum of squares, Mean square	To the 4 decimal places
	α, β, ρ	4 significant digits

	F-value	To the 2 decimal places the following also applies: if F-value<0.01, displayed "F<0.01".
	p-value	To the 4 decimal places 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

5.5 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%.

5.6 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.

5.7 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 body weight, BMI, Child-Pugh score and clinical laboratory values including eGFR 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.

Body weight will be the value obtained at Day -1.

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

7. STATISTICAL METHODOLOGY

7.1 Disposition of Subjects

Disposition of subjects will be listed.

- Number and percent of subjects completed and discontinued protocol scheduled visits with its reason 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 by each group (Groups 1, 2 and 3) and overall. 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
	Child-Pugh score on Day -1	Metric
	Smoking habits	Binary
	Alcohol consumption habits	Binary
	Medical history	Binary
	Complications	Binary

Child-Pugh score will be summarized only in subjects with hepatic impairment.

All data related to Child-Pugh classification will be listed.

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) and overall. Prior and concomitant medications will be summarized separately. Incidence tables will be summarized with ATC Level 2 code, text and Drug Code, Drug Name.

Prior medication is any medication taken within 30 days of Screening. Concomitant medication is defined as any medication, other than the IMP, which is taken during the study, including prescription and over the counter medications. All concomitant medications used from the Screening visit to the last scheduled visit must be recorded in the CRFs with their daily dosage, route, duration, and reasons for administration.

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.

7.7.10 Handling of re-examination data

For the re-examination at screening, the examination value of the re-examination at the point closest to date of IMP is adopted.

If there is unscheduled data after the date of IMP, it will be excluded from calculation of summary statistics and frequency aggregation.

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 hepatic 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 Child-Pugh score, Child-Pugh classification (Normal, Mild, Moderate), albumin, bilirubin, prothrombin and eGFR (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 (Child-Pugh score, Child-Pugh classification, albumin, bilirubin, prothrombin time and eGFR) plot will be produced for all subjects overlaid in one graph.

Child-Pugh score will be plotted only in subjects with hepatic impairment.

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 hepatic impairment group (Group 1 or 2) compared to the normal hepatic 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 and time.

AE Occurrence from Start of IMP = Date/Time of Onset- Start Date/Time of Administration.
If Time is Missing, Date of Onset - Date of Administration +1.

Duration of AE = Date/Time of Resolution - Date/Time of Onset.
If Time is Missing, Date of Resolution - Date of Onset +1.

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

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.

The frequency and incidence of TEAEs will be summarized by System Organ Class (SOC), 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.

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 and Body Weight

All vital sign data will be listed.

Vital signs (body 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. Overall evaluation will be summarized using frequency and percentage.

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.

7.9.7 Other Safety Assessments

Not applicable in the study.

8. CHANGES FROM THE PROTOCOL

We will not summarize the numbers (occurrences) of TEAEs.

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.
2. FDA Guidance for Industry– Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling. May 2003

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
	List of Child-Pugh classification	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 Protein Binding Rate and Free Fraction	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

No.	Title of listing	Analysis Population/Dataset
	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 Protein Binding Rate and Free Fraction	PK
	Descriptive Statistics for Plasma Pharmacokinetic Parameters	PK
	Estimate of the Ratio of Geometric LSmeans for pharmacokinetic parameters of each hepatic impairment group (Groups 1 and 2) with relative to the normal hepatic 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 (Child-Pugh score, Child-Pugh classification, Albumin, Bilirubin, Prothrombin Time and eGFR) plot for all subjects overlaid in one graph	PK
16.2.6 – Pharmacokinetics		
	Profile of Individual Plasma Concentrations	PK

13. REVISION HISTORY FOR SAP AMENDMENTS

Version 2.0 (9 October, 2018)

It reflected the results of the data review meeting on 25 September, 2018.

In Section 5.3, the PK analysis excluding possible outliers conduct for secondary/sensitivity analysis has been added.

In Section 7.7.10, a description concerning the Handling of re-examination data has been added.

In Section 7.9.1, the method to calculate the duration of the AE and the time from start of the IMP to AE occurrence has been changed from date to date/time.

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 $AUC_{0-last} = \sum_{i=1}^{n} \frac{t_i - t_{i-1}}{2}(C_{i-1} + C_i)$
$AUC_{0-\infty}$	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]		