Statistical Analysis Plan

Protocol No. MCI-186-E05

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

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APPROVAL FORM

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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALT	alanine transaminase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BDR	blinded data review
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CV	coefficient of variation
DP	decimal places
DMC	data monitoring committee
ECG	electrocardiogram
FAS	full analysis set
ITT	intent-to-treat
LLOQ	lower limit of quantitation
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model repeated measures
PD	pharmacodynamics
PDPOP	PD Population
PK	pharmacokinetics
PKPOP	PK Population
PP	per protocol
PT	preferred term
RAND	all subjects randomized population
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse events
ULN	upper limit of normal range
WHO	World Health Organization

LIST OF PK AND/OR PD PARAMETERS

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
$AUCu_{0\text{-}\infty}$	h•ng/mL	Unbound area under the concentration-time curve from time zero to infinity with extrapolation of the terminal phase
$AUC\%_{ex}$	%	Area under the plasma concentration-time curve extrapolated from the last quantifiable concentration time point to infinity in % of the total $AUC_{0\text{-}\infty}$
C_{max}	ng/mL	Maximum plasma concentration after administration
C_{last}	ng/mL	Last quantifiable concentration
CL	L/h	Total clearance
CLu	L/h	Unbound total clearance
λ_z	/h	Elimination rate constant from the central compartment
Lower limited of λ_z	h	Lower data point used for the estimation of λ_z
MRT	h	Mean residence time
Number of λ_z points	-	Number of data point used for the estimation of λ_z
$t_{1/2}$	h	Terminal elimination half-life in plasma concentration-time course
t_{max}	h	Time of maximum plasma concentration after administration
Upper limited of λ_z	h	Upper data point used for the estimation of λ_z
V_{ss}	L	Volume of distribution at steady state
V_z	L	Volume of distribution during terminal phase

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol (v3.0) dated 06-FEB-2019. The plan covers statistical analysis, tabulations and listings of the study data to investigate the pharmacokinetics of MCI-186 in subjects with severe hepatic impairment compared to subjects with normal hepatic function.

Any statistical analysis details described in this document supersede any description of statistical analysis in the protocol.

2. STUDY OBJECTIVE AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

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

2.1.2. Secondary Objective

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

2.2. Study Endpoints

2.2.1. Primary Endpoints

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

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

2.2.2. Secondary Endpoints

The following secondary endpoints will be evaluated during the study:

Pharmacokinetic parameters of MCI-186:

- $t_{½}$
- Time to reach peak concentration (t_{max})
- Terminal elimination rate constant (λ_Z)
- Total clearance (CL)
- Volume of distribution at steady state (V_{ss})
- Volume of distribution during the terminal phase (V_Z)

- Mean residence time (MRT)
- Unbound area under the concentration-time curve from time zero to infinity ($AUCu_{0-\infty}$)
- Unbound total clearance (CLu)

Pharmacokinetic parameters of the sulfate conjugate:

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

Safety and Tolerability

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Physical examination
- Vital signs (blood pressure, pulse rate and body temperature)
- 12-lead electrocardiogram (ECG) parameters
- Laboratory assessments including biochemistry, haematology, coagulation and urinalysis
- Columbia-Suicide Severity Rating Scale (C-SSRS; see Appendix 1 in Section 14 of the Protocol)

3. STUDY DESIGN

3.1. Study Design

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

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

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

Order of subject enrolment

Individual matching of healthy subjects will be performed for the subjects with hepatic impairment. Therefore, after the end of study assessments are completed in subjects with hepatic impairment, healthy subjects will be enrolled. Each healthy subject will be individually

matched with a hepatic impairment subject with respect to age (±15 years), body weight (±20%) and gender. Matched healthy subjects may be recruited by any study site, not necessarily by the same site which recruited the subject with hepatic impairment.

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

Study periods and duration of study

The study consists of:

- A pre-admission Screening period (Day -21 to Day -2)
- A treatment hospitalisation period (Day -1 to Day 3) with single IV infusion of 30 mg MCI-186 over 60 minutes (including an infusion time window of ±3 minutes) on Day 1, and PK blood sampling until 48 hours post-dose.

  All subjects will be confined to the study centre from Day -1 to Day 3. Safety assessments will be performed until discharge.
- A Follow-up Period (Day 7 + 2 days). An end of study assessment will be performed.

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

3.2. Schedule of Study Procedures

Study assessments are summarised in the time and events schedule (Table 1).

Table 1 Time and events schedule

Study Period	**Screening**	**Treatment Hospitalisation**																**Follow-up**
Study Day	**-21 to -2**	**-1**	**1**													**2**		**3**	**7 (+2)**
Time point			[redacted]																
Informed consent	X																		
Confinement		←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	
Outpatient	X																		X
Inclusion/exclusion criteria	X	X	X																
Demography & medical history	X																		
Physical examination	X	X	X[2]													X[2]		X	X[2]
Weight	X	X														X		X	X
Height	X																		
BMI	X	X																	
Vital signs	X	X	X													X		X	X
12-lead ECG	X	X	X													X		X	X
Urine drugs of abuse & breath alcohol test	X	X																	
Biochemistry, haematology, coagulation & urinalysis	X	X														X		X	X
C-SSRS		X														X			

Study Period	**Screening**	**Treatment Hospitalisation**																**Follow-up**
Study Day	**-21 to -2**	**-1**	**1**													**2**		**3**	**7 (+2)**
Time point			[redacted]																
Hepatic impairment assessment (Child-Pugh classification; Group 1 only)	X	X																	
eGFR	X	X														X		X	X
Hepatitis B & C and HIV	X																		
Pregnancy test in females	X	X																	X
Protein binding blood sampling		X																	
IMP administration				←			→												
PK sampling (blood)[3]			[redacted]																
AE and concomitant medications	←																		→

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

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

- [redacted] ±15 minutes

3.3. Sample Size and Power Considerations

The planned sample size of 6 evaluable subjects with severe hepatic impairment and 6 evaluable healthy subjects is not based on a power calculation, but is based on the FDA recommendation for at least 6 evaluable subjects per group[1].

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

4. PLANNED ANALYSIS

4.1. Interim Analysis

No interim analysis is planned for this study.

4.2. Final Analysis

This SAP will be finalized before database lock. Final data analysis will be conducted after database lock.

5. ANALYSIS POPULATIONS

Analysis Population	Definition
Safety analysis set (SAF)	All subjects who receive at least one dose of IMP
PK analysis set (PKPOP)	All subjects, who have received at least one dose of IMP and for whom the PK data are considered sufficient and interpretable.

PK=pharmacokinetic

The SAF or All subjects will be used for study population-related evaluations. The SAF will be used for all safety evaluations. The PKPOP will be used for the PK analyses.

6. STATISTICAL CONSIDERATIONS

6.1. Descriptive Statistics

(1) Non-PK related

Continuous data will be summarized descriptively using the number of subjects in the analysis set (N), the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis population being presented, unless otherwise specified.

(2) PK related

Plasma concentrations will be summarized descriptively using N, n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%.

The plasma and urine PK parameters will be summarized descriptively using N, n, arithmetic mean, SD, median, minimum, maximum, CV%, geometric mean and geometric CV%

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

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

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

where σ represents the standard deviation computed on the natural logarithmic transformed concentrations.

6.2. Statistical Tests

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

7. DATA CONVENTIONS

7.1. Analysis Variable Definitions

7.1.1. Study Subjects

7.1.1.1. Protocol Deviations

Protocol deviations will be identified and documented during a data review prior to database lock and confirmed by database lock. Important protocol deviations will be defined as important deviations that may significantly impact the completeness, integrity, accuracy, and/or reliability of the study data and may significantly affect a subjects rights, safety, or well -being.

7.1.1.2. Demographic and Other Baseline Characteristics

(1) BMI

BMI will be recalculated using the formula below and reported to 1dp.

BMI (kg/m^2) = weight at screening (kg) / {height at screening (m)}^{2}

(2) Child-Pugh Classification

The maximum score a subject can get from the classification will be 14 and not 15. This is because subjects with severe encephalopathy will be excluded from the trial (exclusion criteria

19), so the maximum score a subjects can get from the 'Hepatic Encephalopathy' question is 2 and not 3, hence the maximum score obtainable will be 14 and not 15.

7.1.1.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or later.

7.1.1.4. Prior or Concomitant Medication

Medications will be coded according to the World Health Organisation Drug Dictionary (WHO-DD) SEP 2018 version.

(1) Prior Medication

Prior medication is any medication that was stopped prior to administration of IMP.

(2) Concomitant Medication

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

7.1.2. Safety Assessments

7.1.2.1. Adverse Events

Adverse events will be coded according to the MedDRA version 21.1 or later.

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

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

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical events

(1) Treatment Emergent Adverse Events/ Treatment Emergent Serious Adverse Events (TEAEs/TESAEs)

AEs/SAEs will be classified as 'treatment-emergent' if they arise following the first administration of IMP or if a pre-dose AE increases in severity following dosing.

(2) Adverse Drug Reaction

A TEAE is considered an "adverse drug reaction" if it has been assessed as having a "reasonable possibility" in relationship to the study drug.

(3) Duration of Adverse Events

Duration of Adverse Events (days) = AE stop date – AE start date + 1

7.1.2.2. 12-Lead ECG

(1) Criteria for pre-defined limit

12-lead ECG:

- QTcF : ≤ 450 msec, 450 < QTcF ≤ 480 msec, 480 < QTcF ≤ 500 msec, > 500 msec
- Change from baseline in QTcF : > 30 msec, > 60 msec

7.1.3. Pharmacokinetics Evaluation

7.1.3.1. Plasma Concentration

For the calculation of the summary statistics, concentration values reported as below the limit of quantification (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. LLOQ for sulfate is not defined because sulfate conjugates are determined as Unchanged MCI-186 after hydrolysis. Howerer "253.25 / 174.20" will be expediently used as LLOQ of sulfate only to calculate the geometric mean and geometric CV%.

7.1.3.2. Pharmacokinetic Parameters

(1) Below the limit of quantification

For the calculation of PK parameters, actual sampling time (in hours rounded to 2 decimal places) relative to dosing should be used. Concentration below the limit of quantification (BLQ) will be imputed with a value of 0. For calculation of AUCs, missing data will be treated as if the respective sample never had been scheduled for the calculation by the linear-linear trapezoidal rule.

7.2. Analysis Visit Definitions

(1) Non-PK related

The date of the first dose of study drug is defined as Day 1.

Unless otherwise specified, baseline will be the last observed value of the parameter of interest prior to the first intake of study drug on Day 1 (this includes unscheduled visits). For other visits, if there are multiple data in a window, the closest data to nominal day will be used. If the distance to the nominal day is the same, the data of later date will be used.

(2) PK related

The allowable time window will be the following.

Pre-dose	Within 30 to 60 minutes before dosing
[redacted]	Scheduled time ± 5 minutes
[redacted]	Within 3 minutes after dosing

[redacted]	Scheduled time ± 5 minutes
[redacted]	Scheduled time ± 15 minutes

7.3. Data Handling Convention for Missing Data

(1) Non-PK related

Adverse events:

If severity or relationship is found to be missing the most severe occurrence will be imputed for the summary of interest.

For AE start missing or partial dates, the AE will be treated as TEAE if it cannot be determined to be a non-TEAE.

Other Safety-related endpoints:

For other safety-related summaries, only observed data will be used. Unless otherwise specified, missing safety data will not be imputed.

(2) PK related

For PK summaries, only observed data will be used. Missing PK data will not be imputed.

8. STATISTICAL METHODOLOGY

8.1. Study Subjects

8.1.1. Subject Disposition

Subject disposition will be summarized on the SAF (*Table 14.1.1*).

Subject disposition will be listed on the SAF (*Listing 16.2.1*). Inclusion and exclusion criteria deviation at screening will be listed on All Subjects (*Listing 16.2.2.1*).

8.1.2. Analysis Populations

Analysis populations will be summarized (*Table 14.1.2*).

Analysis populations will be listed on the SAF (*Listing 16.2.3*).

8.1.3. Protocol Deviations

Important Protocol Deviations will be listed on the SAF (*Listing 16.2.2.2*).

8.1.4. Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be used.

	Category	**Descriptive**
Sex	Male, Female	
Age (years)	18 – 65 > 65	Yes
Height (cm)		Yes

Weight (kg)		Yes
BMI (kg/m^2)		Yes
Race	American Indian or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Multiple, Other	
Ethnicity	Not Hispanic or Latino, Hispanic or Latino, Unknown	
eGFR on Day -1		Yes
Child-Pugh Score on Day -1		Yes
Alcohol Consumption	Never drank, Former drinker, Current drinker	

Demographic and other baseline characteristics will be summarized on the SAF (*Table 14.1.3*). Demographic data will be listed on the SAF (*Listing 16.2.4.1*) and other baseline characteristics (including alcohol consumption) will be listed on the SAF (*Listing 16.2.4.2*). Child-Pugh classification data will be listed on the SAF (*Listing 16.2.4.3*) for hepatically impaired subjects only.

8.1.5. Medical History

Medical history data will be listed on the SAF *(Listing 16.2.4.4)*. Other Screening and Day -1 assessments (alcohol breath test) will be listed on the SAF *(Listing 16.2.4.5)*.

8.1.6. Prior or Concomitant Medications

Prior medication and concomitant medication will be summarized separately on the SAF (*Table 14.1.4 and Table 14.1.5*).

Prior and concomitant medication will be listed on the SAF (*Listing 16.2.5.1*).

8.1.7. Study Drug Administration

Study drug administration will be listed on the SAF (*Listing 16.2.5.2*).

8.2. Safety Assessments

Safety assessments will be made on the SAF population.

8.2.1. Adverse Events

Overall summary including the following will be presented (*Table 14.3.1.1*).

- Subjects with at least one AE
- Subjects with at least one SAE
- Subjects with at least one TEAE
- Subjects with at least one TESAE
- Subjects with at least one adverse drug reaction
- Subjects with at least one serious adverse drug reaction

- Subjects with at least one TEAE leading to discontinuation of study drug
- Subjects with at least one TESAE leading to discontinuation of study drug
- Subjects with at least one adverse drug reaction leading to discontinuation of study drug
- Subjects with at least one serious adverse drug reaction leading to discontinuation of study drug

The following summaries also will be conducted.

- TEAEs by SOC and PT (*Table 14.3.1.2*)
- TESAEs by SOC and PT (*Table 14.3.1.3*)
- Adverse drug reactions by SOC and PT (*Table 14.3.1.4*)
- TEAEs by SOC, PT and severity (*Table 14.3.1.5*)
- TEAEs by SOC, PT and relationship to study drug (*Table 14.3.1.6*)

Each of the summaries will be done at the subject level - 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 severity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility/no reasonable possibility) and/or the earliest duration. If intensity or relationship is found to be missing, the most severe occurrence will be imputed for that particular summary.
These summaries will also present the number of events that occurred, and multiple occurrences of the same event within a subject will all be accounted for in the maximum intensity category and maximum relationship category they were classed as.
The following will be listed.

- All AEs (*Listing 16.2.7*)
- Death (only if any deaths occur)

8.2.2. Laboratory Tests

Laboratory test reference ranges will be listed *(Listing 16.2.8.1)*.
Abnormal results (categorised as high, low and abnormal) will be listed for the following laboratory tests parameters.

Laboratory Test	Parameters
Hematology (*Listing 16.2.8.2.X*)	Haemoglobin, Haematocrit, Platelet Count, Red Blood Cell Count, Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), White Blood Cell Count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
Biochemistry (*Listing 16.2.8.3.X*)	Alkaline phosphatase, Aspartate aminotransferase, Alanine aminotransferase, Gamma-glutamyl transpeptidase, Potassium, Sodium, Chloride, Inorganic phosphate, Glucose, Urea, Bilirubin (direct and total), Cholesterol, Triglycerides, High density

	lipoprotein-cholesterol, Low density lipoprotein-cholesterol, Protein (total), Albumin, Creatine kinase, Creatinine, Follicile-stimulating hormone (FSH)[1], Human Chorionic gonadotrophin (hCG)[2]
Coagulation (*Listing 16.2.8.4.X*)	Prothrombin time, International normalised ratio, Activated partial thromboplastin time
Urinalysis (*Listing 16.2.8.5.X*)	Specific gravity, pH, Protein, Glucose, Ketones, Urobilinogen, Human chorionic gonadotropin (hCG)[2], Microscopic examination[3]
Serology (*Listing 16.2.8.6.X*)	Hepatitis B surface antigen, Hepatitis C virus antibody, Human immunodeficiency virus antigen/antibodies

[1] Females only; performed at Screening only

[2] Females only; a serum pregnancy test will be performed at Screening and a urine pregnancy test at all other time points

[3] Performed only if required, based on urinalysis results

Summary tables for certain laboratory test parameters may be performed upon review of data depending on the number of abnormal values observed. Baseline will be Day -1.

8.2.3. Vital Signs

Absolute values and changes from baseline will be summarized (*Table 14.3.2.1*) and shift table of clinically relevant categories will be presented (*Table 14.3.2.2*) for the following parameters.

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Body Temperature (°C)

Baseline will be Day 1 pre-dose.

All data will be listed (*Listing 16.2.9.1*).

8.2.4. 12-Lead ECGs

Absolute values and changes from baseline will be summarized (*Table 14.3.3.1*) and shift table of clinically relevant categories will be presented (*Table 14.3.3.2*) for the following parameters.

- Heart Rate (bpm)
- PR (msec)
- RR (msec)
- QRS (msec)
- QT (msec)
- QTcF (msec)

The frequency counts and percentages of subjects with 12-lead ECG values outside pre-defined limit will be summarized (*Table 14.3.3.3*).

Baseline will be Day 1 pre-dose.

All data will be listed (*Listing 16.2.9.2*).

8.2.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

C-SSRS data will be listed (*Listing 16.2.9.3*).

8.2.6. Estimated Glomerular Filtration Rate (eGFR)

eGFR data will be listed (*Listing 16.2.9.4*).

8.2.7. Physical Examinations

Physical examination body systems examined at Screening, Day -1 and Day 3 will be the following:

- Abdominal
- Cardiovascular
- Gastrointestinal
- General appearance
- Eyes, Ears, Nose and Throat
- Head and Neck
- Hepatic
- Lymph Nodes
- Musculoskeletal
- Neurological
- Dermatological
- Respiratory
- Other

Abbreviated physical Examination body systems examined at all other visits.
All data will be listed (*Listing 16.2.9.5*).

8.3. Pharmacokinetics Evaluation

8.4.1 Plasma Concentration

All measured plasma concentrations will be listed (*Listing 16.2.6.1* and *Listing 16.2.6.2*).
All measured protein binding rate and free fraction will be listed (*Listing 16.2.6.3*)
Plasma concentrations will be summarized at each scheduled sampling time point by each group (Groups 1 and 2) (*Table 14.2.1.1* and *Table 14.2.1.2*).
Protein binding rate and free fraction will be summarized by each group (Group 1 and 2). (*Table 14.2.2*)
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 and 2) overlaid in one graph (*Figure 14.2.4.1*, *Figure 14.2.4.2*, *Figure 14.2.5.1* and *Figure 14.2.5.2*).
2. Mean concentration-time plot for each group (Groups 1 and 2) overlaid in one graph

(*Figure 14.2.1.1*, *Figure 14.2.1.2*, *Figure 14.2.2.1* and *Figure 14.2.2.2*).

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.

8.4.2 Pharmacokinetic Parameters

The pharmacokinetic parameters listed in Section 2.2 will be calculated for each subject on active dose using non-compartmental model. All PK parameters will be listed (*Listing 16.2.6.4* and *Listing 16.2.6.5*).

The PK parameters will be summarized by each group (Groups 1 and 2). 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% (*Table 14.2.3.1* and *Table 14.2.3.2*).

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

- tmax: will be presented with 2 decimal places.
- Cmax: will be presented with the number of significant digits they are reported with.
- Number of λz points: will be presented with integer.
- 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.

- Cmax: 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 $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, $AUC_{u0\text{-}\infty}$ and Cmax (on the verticalaxis) versus Child-Pugh score, Child-Pugh classification (Normal, Severe), albumin, bilirubin, prothrombin and eGFR (on the horizontal axis) with regression line, will be produced in linear scales:

The PK parameters of ($AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, $AUC_{u0\text{-}\infty}$ and C_{max} of MCI-186 and the sulfate conjugate) vs (Child-Pugh score (*Figure 14.2.3.1.1 and Figure 14.2.3.2.1)*, Child-Pugh classification (*Figure 14.2.3.1.2 and Figure 14.2.3.2.2)*, albumin (*Figure 14.2.3.1.3 and Figure*

14.2.3.2.3), bilirubin (*Figure 14.2.3.1.4 and Figure 14.2.3.2.4)*, prothrombin time (*Figure 14.2.3.1.5 and Figure 14.2.3.2.5)* and eGFR (*Figure 14.2.3.1.6 and Figure 14.2.3.2.6)*) plot will be produced for all subjects overlaid in one graph.

Following log-transformation, C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ of MCI-186 and the sulfate conjugate will be separately analysed using a mixed effects model with treatment as a fixed effect. Example SAS code:

```
proc mixed;
class subject treatment;
model log(endpoint) = treatment / solution ddfm=kr outpm=pred;
lsmeans treatment / diff cl alpha=0.1;
run;
```

The point estimates and their corresponding 90% CIs on the log scale will then be back-transformed to provide point estimates and 90% CIs for the ratios of severe hepatic impairment / normal hepatic function (*Table 14.2.4.1 and Table 14.2.4.2*).

9. DATA PRESENTATION CONVENTIONS

9.1. Number of Digits to Report

(1) Non-PK related

Statistic	Specification	Apply to
Minimum, Maximum	Same number of DPs as the data provided in the datasets	All original (i.e. non-derived)
	see section 7.3	All derived data
Mean, Median, SD, SE, Confidence intervals	One more DP than above	All
Percentages*1	1 DP	All
Ratios	3 DPs	All
p-values*2	3 DPs	All

*1 Percentages: use 1 DP, except for the following cases:

If the percentage is equal to 0, then leave blank, do not use (0)

If the percentage is equal to 100, then use "(100)" without a decimal

*2 p-values: use 3 DP, except for the following cases:

If the p-value is less than 0.01, then use $p<0.01$

9.2. Treatments to Report

Treatment	For TFLs
MCI-186 30 mg / 100 mL Severe Hepatic Impairment	MCI-186 30 mg / 100 mL Severe
MCI-186 30 mg / 100 mL Normal Hepatic Function	MCI-186 30 mg / 100 mL Normal

9.3. Analysis Visits to Report

(1) Non-PK related

Safety:

Analysis Visit	Apply to		
	Laboratory Tests	Vital Signs	12-Lead ECGs
Screening	X	X	X
Day -1 / Baseline	X	X	X
Day 1 / Baseline		X	X
Day 2	X	X	X
Day 3	X	X	X

Unscheduled visits, retests (same visit number assigned) and follow-up visits will not be displayed in by-visit summary tables, but will be included in the data listings.

10. CHANGE FROM THE PROTOCOL

There are currently no changes to the analysis from the protocol.

11. SOFTWARE

All statistical analyses will be performed using SAS® version 9.3 or higher.

The PK parameters will be calculated using WinNonlin® software (version 6.3 or later).

12. REFERENCES

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

Appendix 1 Pharmacokinetic Parameter Calculations

- Actual blood sampling times will be used in the calculation of pharmacokinetic parameters
- All concentrations below the LLOQ will be set at zero for pharmacokinetic calculations
- When k_{el} is missing (or cannot be determined), $t_{1/2}$, $AUC_{0-\infty}$, $AUC\%_{ex}$, CL/F, MRT, V_z/F and V_{ss}/F will not be calculated.

PK Parameter Calculations		
Parameters	Unit	Calculation
C_{max}	ng/mL	will be determined by visual inspection
$AUC_{0-\infty}$	ng·h/mL	$AUC_{0-\infty} = AUC_{0-last} + C_{last} / k_{el}$ C_{last}: last measurable concentration
$AUC\%_{ex}$	%	$AUC\%_{ex} = (AUC_{0-\infty} - AUC_{0-last}) / AUC_{0-\infty} \times 100$
AUC_{0-last}	ng·h/mL	will be calculated using the linear trapezoidal method and actual times $$AUC_{0-last} = \sum_{i=1}^{n} \frac{t_i - t_{i+1}}{2} (C_{i-1} + C_i)$$
t_{max}	h	Measured time of C_{max}
$t_{½}$	h	$t_{½}$ will be determined as: $t_{½} = \log_e (2) / k_{el}$
k_{el}	/h	The exponential rate constant of the terminal phase, k_{el}, will be estimated by log-linear regression, if determinable. The number of data points included in the regression will be determined by visual inspection. Wherever possible, a minimum of 3 data points will be used in the estimation of k_{el}. During the analysis, this calculation method repeats regressions using the last three points with non-zero concentrations, then the last four points, last five, etc. The time of maximum concentration (tmax) will be excluded from the estimation of k_{el}. Points with a value of zero for the dependent variable are excluded. For each regression, an adjusted R^2 is computed $$Adjusted\ R^2 = 1 - \frac{(1 - R^2) \times (n - 1)}{(n - 2)}$$ where n is the number of data points in the regression and R^2 is the square of the correlation coefficient. The regression with the largest adjusted R^2 is selected to estimate k_{el}, with these caveats: - If the adjusted R^2 does not improve, but is within 0.0001 of the largest adjusted R^2 value, the regression with the larger number of points is used. - k_{el} must be positive, and calculated from at least three data points.

CL/F	L/h	CL/F = Dose / $AUC_{0-\infty}$
MRT	/h	MRT = $AUMC_{0-\infty}$ / $AUC_{0-\infty}$ $AUMC_{0-\infty}$: area under the first moment curve extrapolated to infinity