



## STATISTICAL ANALYSIS PLAN

**FMGX-CP-109**

**A Phase 1, randomized, single-center, double-blind, placebo-controlled study of fosmanogepix administered as single and multiple doses in healthy adult Chinese subjects**

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## LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC <sub>0-24h</sub>	Area under the concentration-time curve from time 0 to 24 hours
AUC <sub>extrap</sub>	Proportion of AUC <sub>inf</sub> due to extrapolation
AUC <sub>inf</sub>	Area under the concentration-time curve from time 0 to infinity
AUC <sub>inf,iv</sub>	Area under the concentration-time curve after IV infusion from time 0 to infinity
AUC <sub>inf,po</sub>	Area under the concentration-time curve after oral administration from time 0 to infinity
AUC <sub>last</sub>	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration
AUC <sub>tau</sub>	Area under the concentration-time curve at steady state over the dosing interval tau
AUC <sub>tau,iv</sub>	Area under the concentration-time curve at steady state after IV infusion over the dosing interval tau
AUC <sub>tau,po</sub>	Area under the concentration-time curve at steady state after oral administration over the dosing interval tau
BID	Twice daily
BLQ	Below the quantifiable limit
BMI	Body mass index
CL	Total clearance of drug
CL/F	Apparent oral clearance
C <sub>max</sub>	Maximum plasma concentration
CNS	Central nervous system
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
C <sub>trough</sub>	Pre-dose concentration
CV	Coefficient of variation
DILI	Drug-induced liver injury

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ECG	Electrocardiogram
eCRF	electronic CRF
F	Absolute bioavailability
$f_u$	Fraction unbound
IV	Intravenous(ly)
$k_{el}$	First-order elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic(s)
PT	Preferred term
QD	Once daily
QTcF	QT corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SMQ	Standardized MedDRA Queries
$t_{1/2}$	Terminal phase half-life
TBili	Total bilirubin
TEAE	Treatment-emergent AE
$T_{max}$	Time to first occurrence of $C_{max}$
$V_{ss}$	Steady-state volume of distribution
$V_z/F$	Apparent volume of distribution for extravascular dosing
WHO DDE	World Health Organization Drug Dictionary Enhanced

## 1 INTRODUCTION

This document outlines the statistical methods to be implemented in the analysis of data collected within the scope of Basilea Pharmaceutica International Ltd, Allschwil, Protocol FMGX-CP-109, a Phase 1, randomized, single-center, double-blind, placebo-controlled study of fosmanogepix administered as single and multiple doses in healthy adult Chinese subjects.

The purpose of this Statistical analysis plan (SAP) is to define the planned statistical methods in line with the study objectives. This plan should be read in conjunction with the protocol Version 3.0 (18 March 2025). All analyses will be conducted using SAS® Version 9.4 or higher.

## 2 OBJECTIVES

### 2.1 Primary objective

The primary objective of the study is to evaluate the pharmacokinetics (PK) profile of manogepix (active moiety of fosmanogepix) after single dose administration (Part-1) and after repeated doses (Part-2) in healthy adult Chinese subjects.

### 2.2 Secondary objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of fosmanogepix in healthy adult Chinese subjects (Part-1 and Part-2).
- To evaluate the PK profile of fosmanogepix (pro-drug of manogepix) after single dose administration (Part-1) and after repeated doses (Part-2) in healthy adult Chinese subjects.
- To evaluate the plasma protein binding of manogepix (active moiety of fosmanogepix) after single dose administration in healthy adult Chinese subjects (Part-1).

## 3 INVESTIGATIONAL PLAN

### 3.1 Overall study design

This is a Phase 1 PK, safety and tolerability study of fosmanogepix in healthy adult Chinese subjects, conducted in two parts: Part-1 Single-dose and Part-2 Multiple-dose. Approximately 52 subjects (32 in Part-1: single-dose and 20 in Part-2: multiple-dose) will be enrolled and randomly assigned to study drug.

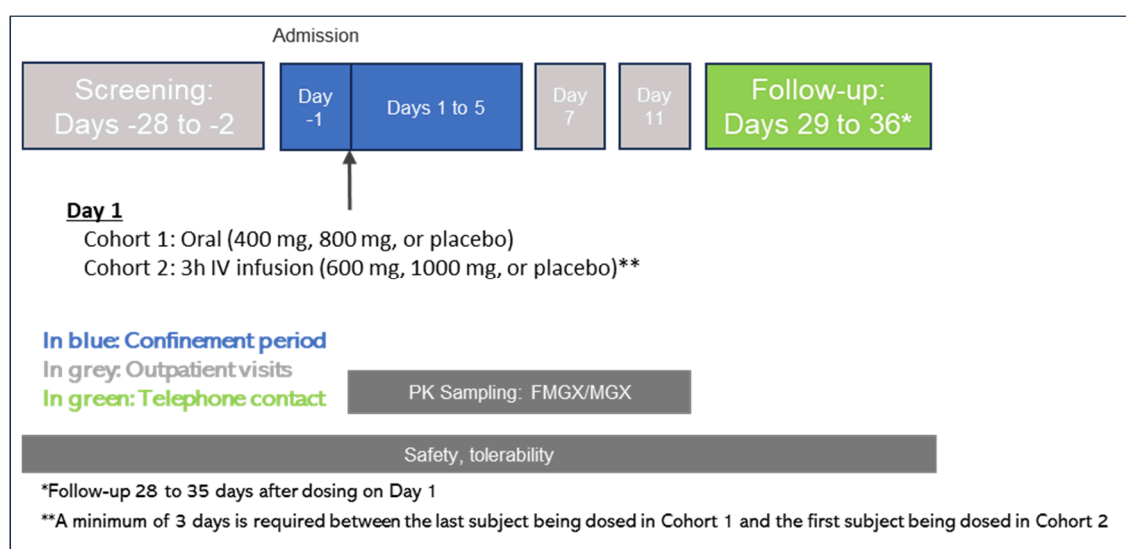
The overall study design is presented as a schematic in Figure 1 and Figure 2. The schedule of assessments is provided in the protocol Section 1.3.

### Part-1: Single-dose part

A total of 32 subjects will be enrolled in Part-1 in two cohorts and randomized to fosmanogepix (with a low dose and a high dose in each cohort, administered in parallel) or placebo. This part will have a randomized, double-blind, parallel single-dose design. In each cohort, subjects will receive fosmanogepix or placebo by either oral administration (Cohort 1) or as a 3-hour intravenous (IV) infusion (Cohort 2). Six subjects in each cohort will be randomized to a low dose of fosmanogepix, six subjects will be randomized to a high dose of fosmanogepix, and four subjects will be randomized to placebo.

The total duration of participation in Part-1 is up to 64 days, comprising a screening period of up to 28 days, a total treatment and observation duration of 11 days (1 day of dosing and a 10-day full PK profile after dosing), and a follow-up call 28 – 35 days after dosing.

**Figure 1 Part-1 study design**



### Part-2: Multiple-dose part

A total of 20 subjects will be enrolled in Part-2 in two cohorts and randomized to fosmanogepix or placebo. This part will have a randomized, double-blind, parallel multiple-dose design. All subjects in Cohort 3 and Cohort 4 will receive a 3-hour IV infusion twice daily (BID) 12 hours apart on Day 1. In Cohort 3, subjects will receive the maintenance dose via a 3-hour IV infusion, once daily (QD) from Day 2 to Day 7. In Cohort 4, subjects will receive the maintenance dose via a 3-hour IV infusion, QD on Day 2 and Day 3, and switch to oral administration QD from Day 4 to Day 7. Eight subjects in each cohort will be randomized to fosmanogepix and two subjects will be randomized to placebo.

The total duration of participation in Part-2 is up to 70 days, comprising a screening period of up to 28 days, a treatment and observation duration of 22 days (7 days of dosing and a

15-day full PK profile after the last dose), and a follow-up call 28 – 35 days after the last dosing.

**Figure 2 Part-2 study design**



## 3.2 Study endpoints

### 3.2.1 Primary endpoints

The primary endpoints are the plasma PK parameters for manogepix including:

- Part-1 (Single-dose):
  - $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-24h}$ ,  $AUC_{last}$ ,  $AUC_{inf}$
  - CL (or CL/F for Cohort 1),  $V_{ss}$  (or  $V_z/F$  for Cohort 1),  $t_{1/2}$ , F as permitted by data.
- Part-2 (Multiple-dose):
  - $C_{max}$ ,  $T_{max}$ ,  $AUC_{tau}$  on Day 7
  - CL (or CL/F for Cohort 4),  $V_{ss}$  (or  $V_z/F$  for Cohort 4),  $t_{1/2}$ , F after last dose administration on Day 7 as permitted by data
  - $C_{trough}$  (Trough concentration) on Day 1 (second dose), Day 2, Day 3, Day 6, Day 7, Day 8 (24 hours after last dose), as permitted by data.

### 3.2.2 Secondary endpoints

The secondary endpoints are:

- Incidence of adverse events (AEs) / serious adverse events (SAEs), clinical safety laboratory tests, vital signs, 12-lead electrocardiogram (ECGs)
- Plasma PK parameters for fosmanogepix including:
  - Part-1 (Single-dose):  $C_{\max}$ ,  $T_{\max}$ ,  $AUC_{0-24h}$ ,  $AUC_{\text{last}}$
  - Part-2 (Multiple-dose):  $C_{\max}$ ,  $T_{\max}$ ,  $AUC_{\text{tau}}$  on Day 7
- Plasma PK parameters for manogepix:
  - Part-1 (Single-dose): Fraction unbound ( $f_u$ ).

## 4 GENERAL STATISTICAL CONSIDERATIONS

Summary outputs will be presented by cohort and treatment as described below:

- Part-1: Oral low dose (Oral 400 mg), Oral high dose (Oral 800 mg), IV low dose (IV 600 mg), IV high dose (IV 1000 mg), Placebo (pooled cohort 1 and cohort 2)
- Part-2: IV only, IV and oral, Placebo (pooled cohort 3 and cohort 4).

Data from Part-1 and Part-2 will be summarized in separate tables and figures.

No formal hypothesis testing will be performed. Continuous data, unless otherwise specified, will be described using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Categorical data will be described using the subject count and percentage in each category. Non-zero percentages will be rounded to one decimal place, except 100%, which will be displayed without any decimal places. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported, up to a maximum of three decimal places. Mean and median will be displayed to one level of precision greater than the data collected, up to a maximum of three decimal places. SD will be displayed to two levels of precision greater than the data collected, up to a maximum of three decimal places.

When count data are presented, the percentage will be suppressed when the count is zero, to draw attention to the non-zero counts. A row denoted 'Missing' will be included in count tabulations where specified in the table shells, to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in the analysis set of interest, unless otherwise specified.

All data will be displayed in listings sorted by cohort, treatment, and subject ID – if applicable, screen failure subjects will be displayed in separately.

## 4.1 Sample size justification

- Part-1 (Single-dose):

A sample size of approximately 16 subjects per cohort (six fosmanogepix low-dose, six fosmanogepix high-dose, four placebo) has been chosen based on the need to minimize first exposure of healthy adult Chinese subjects to study drug, and the requirement to provide adequate PK and safety and tolerability data at each cohort and dose level.

- Part-2 (Multiple-dose):

A sample size of approximately 10 subjects per cohort (eight fosmanogepix, two placebo) has been selected to provide adequate PK and safety and tolerability data for each cohort.

## 4.2 Analysis sets

For purposes of analysis, the following analysis sets are defined.

### 4.2.1 Enrolled set

The enrolled set consists of all randomized subjects. Subjects will be analyzed according to the planned treatment.

### 4.2.2 Safety set

The safety set consists of all randomized subjects who have received at least one dose of study drug. Subjects will be analyzed according to the drug they actually received.

### 4.2.3 Pharmacokinetic set

The PK set consists of all randomized subjects who have received at least one dose of study drug and have at least one post-baseline measurable concentration of manogepix. Subjects will be analyzed according to the drug they actually received.

## 4.3 Other important considerations

### 4.3.1 Definition of baseline

Unless otherwise specified, baseline is defined as the last non-missing assessment prior to the first study drug administration. Both scheduled and unscheduled visits and assessments will be used in determining baseline.

### 4.3.2 Study day calculation and visit windows

Visit windowing approaches will not be used for this study, and visit based summaries will include scheduled assessments only.

The following conventions will be used to calculate analysis study day:

- Day 1 is the day of first study drug administration. Day -1 is the day before Day 1. No Day 0 is defined for this study.

- Prior to Day 1, the algorithm is:  
Study Day = visit/examination date – date of first study drug administration
- For Day 1 and subsequent days, the algorithm is:  
Study Day = visit/examination date – date of first study drug administration + 1.

Summary data such as AEs will not be reported by visit.

Both scheduled and unscheduled visits and assessments will be used to determine minimum and maximum change from baseline. Tables that report abnormalities (e.g., laboratory shift tables) will include all assessments.

#### 4.3.3 Missing and partial data

The following rules for missing data will be followed:

- AE date imputations will follow the rules described in Appendix 1.
- The causality assessment for AEs should not be missing and will be queried for a value. AEs with missing causality will be considered related to study drug.

Unless otherwise specified, missing values for other individual data points will remain missing. Missing values will not be imputed and only observed values will be used in data analyses and presentation.

#### 4.3.4 Duration (e.g., for treatment exposure)

If date and time are collected, then duration is calculated as event end date and time minus event onset date and time. Duration will be displayed as days and fractions of days, or as hours and fractions of hours, as appropriate.

If only the date is collected, then the duration in days is calculated as event end date minus event onset date + 1.

#### 4.3.5 Elapsed actual time

For PK blood sampling, elapsed actual time in hours is the number of hours elapsed from date and time of study drug administration on related day. This time is derived from actual dates and times recorded in the electronic case report form (eCRF).

#### 4.3.6 Coding dictionaries

AEs, medical history, and procedures are to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 28.0 or later. Previous and concomitant treatments are to be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE) dated 01MAR2025 or later (format B3).

## **5 SUBJECT DISPOSITION**

### **5.1 Disposition**

The number and percentage of subjects screened, randomized, and included in each of the analysis sets will be summarized by cohort and treatment. The number and percentage of subjects who completed or discontinued from the study treatment and from study will also be presented, with the reason for discontinuation. All percentages will be based on the number of subjects in the safety set.

Subjects who failed screening and the reasons for screen failure will only be listed.

### **5.2 Protocol deviations**

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The protocol deviations will be categorized as important and non-important deviations. The final list of protocol deviations will be approved prior to database lock and unblinding of the study.

All protocol deviations will be listed.

### **5.3 Inclusion and exclusion criteria**

Full inclusion and exclusion criteria are listed in the protocol Sections 5.1 and 5.2, respectively. Unmet inclusion and met exclusion criteria for each subject will be listed.

## **6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS**

### **6.1 Demographics and general baseline characteristics**

The following demographics and baseline characteristics data will be presented in tables using descriptive statistics for the Safety and PK sets:

- Age, sex, childbearing potential, race, ethnicity
- Height, weight, and body mass index (BMI).

### **6.2 Medical history**

Medical history will only be listed.

## **7 TREATMENTS AND MEDICATIONS**

### **7.1 Prior and concomitant medications/ non-drug procedures**

Prior medications/ procedures are defined as medications/ procedures with a stop date prior to the first dose of study drug. Concomitant medications/ procedures are defined as medications/ procedures that are either ongoing at the start of the first dose of study drug or starting on or after the first dose of study drug.

Prior and concomitant medications and non-drug procedures will only be listed, separately, with each clearly identified as either prior or concomitant.

## 7.2 Study treatments

### 7.2.1 Study drug exposure

Descriptive statistics for the duration of study drug administration will be summarized for the Safety set.

Study drug duration is defined as:

*“Days of (Date of the last dose – Date of first dose) + 1”.*

### 7.2.2 Treatment administration

Treatment administration details will be listed.

## 8 PHARMACOKINETIC ANALYSIS

All PK analyses will be conducted using the PK set.

### 8.1 Plasma concentration

Plasma concentrations of fosmanogepix and manogepix will be analyzed at each time point of collection and will be summarized with descriptive statistics (n, mean, SD, coefficient of variation [CV%], minimum, median, maximum, and geometric mean).

#### *Treatment of outliers*

Individual concentration-time points, if considered anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist and with approval from the Sponsor following a review of the available documentation. Any such exclusion will be outlined in the clinical study report.

Entire individual treatment profiles for a subject may be excluded following review of the available documentation. However, PK analyses may be performed with and without the excluded profiles. Any such exclusion will be clearly listed along with justification for exclusion.

#### *Non-quantifiable concentrations*

All concentration values reported as no results (not collected or not determined) values will be treated as missing. For the calculation of concentration summaries, all concentrations below the quantifiable limit (BLQ) will be treated as 0, except for geometric mean where BLQ values will be ignored. Values that are BLQ will be displayed as ‘BLQ’ in listings. If more than half of the concentrations are BLQ, only minimum, maximum and mean statistics will be calculated, with ‘BLQ’ for minimum and mean.

Plasma concentrations will also be summarized by cohort and treatment with the following figures:

- Plot of geometric mean versus scheduled sampling time, using linear and semi-log scale

- Plot of mean  $\pm$  SD versus scheduled sampling time, using linear and semi-log scale
- Plot of individual concentrations versus actual sampling time, using linear and semi-log scale
- Combined, by cohort and treatment, individual plasma concentrations versus actual sampling time, using linear scale and semi-log scale.

## 8.2 PK parameters

Individual PK parameters will be estimated using non-compartmental methods with WinNonlin®.

The plasma PK parameters will be estimated from the concentration-time profiles. In estimating the PK parameters, BLQ values at the beginning of the profile will be set to zero. BLQ values that occur after the first quantifiable point will be considered missing. Values that are embedded between BLQs, or quantifiable values occurring after two or more BLQs, will be set to missing at the discretion of the pharmacokineticist and in agreement with the Sponsor. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter.

The PK parameters to be determined or calculated using non-compartmental analysis from the plasma concentration-time data are:

**Table 1 Plasma PK parameters for Part-1: Single-dose**

Parameter	Analyte	Definition	Method of determination
AUC <sub>0-24h</sub>	Manogepix/ fosmanogepix*	Area under the plasma concentration-time profile from time zero to 24 hours	Linear/log trapezoidal method.
AUC <sub>last</sub>	Manogepix/ fosmanogepix*	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C <sub>last</sub> )	Linear/log trapezoidal method.
AUC <sub>inf</sub> *	Manogepix	Area under the concentration-time curve from time zero extrapolated to infinite time	AUC <sub>last</sub> + (C <sub>last</sub> */k <sub>el</sub> ), where C <sub>last</sub> * is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis.
C <sub>max</sub>	Manogepix/ fosmanogepix*	Maximum plasma concentration	Observed directly from data.
T <sub>max</sub>	Manogepix/ fosmanogepix*	Time for C <sub>max</sub>	Observed directly from data as time of first occurrence.

Parameter	Analyte	Definition	Method of determination
$t_{1/2}^*$	Manogepix	Terminal elimination half-life	$\text{Log}_e(2)/k_{el}$ , where $k_{el}$ is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
$CL^*$ (Cohort 2 only)	Manogepix	Clearance	$\text{Dose}/AUC_{inf}$ .
$CL/F^*$ (Cohort 1 only)	Manogepix	Apparent clearance	$\text{Dose}/AUC_{inf}$ .
$V_{ss}^*$ (Cohort 2 only)	Manogepix	Volume of distribution at steady state	$CL \times MRT$ , where MRT is the mean residence time calculated for single IV dose as $AUMC_{inf}/AUC_{inf} - (DOF/2)$ , where $AUMC_{inf}$ is the area under the moment curve from time 0 extrapolated to infinity, and DOF is the duration for IV infusion dose.
$V_z/F^*$ (Cohort 1 only)	Manogepix	Apparent volume of distribution	$\text{Dose}/(AUC_{inf} \times k_{el})$ .
$F^*$	Manogepix	Absolute bioavailability	$AUC_{inf,po}(\text{dose normalized})$ (mean value in Cohort 1) / $AUC_{inf,iv}(\text{dose normalized})$ (mean value in Cohort 2)
$f_u$	Manogepix	Fraction of unbound drug in plasma	Obtained from measurement of protein binding (determined by assay lab)

\* As data permit.

**Table 2 Plasma PK parameters for Part-2: Multiple-dose**

Parameter	Analyte	Definition	Method of determination
$AUC_{tau}$	Manogepix/ fosmanogepix*	Area under the plasma concentration-time profile from time zero to the time of the end of the dosing interval (tau), where tau = 24 hours	Linear/log trapezoidal method.
$C_{max}$	Manogepix / fosmanogepix*	Maximum plasma concentration	Observed directly from data.
$T_{max}$	Manogepix / fosmanogepix*	Time for $C_{max}$	Observed directly from data as time of first occurrence.

Parameter	Analyte	Definition	Method of determination
$t_{1/2}^*$	Manogepix	Terminal elimination half-life	$\text{Log}_e(2)/k_{el}$ , where $k_{el}$ is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
$CL^*$ (Cohort 3 only)	Manogepix	Clearance	$\text{Dose}/AUC_{\tau}$ .
$CL/F^*$ (Cohort 4 only)	Manogepix	Apparent clearance	$\text{Dose}/AUC_{\tau}$ .
$V_{ss}^*$ (Cohort 3 only)	Manogepix	Volume of distribution at steady state	$CL \times MRT$ , where MRT is the mean residence time calculated as $[AUMC_{\tau} + \tau(AUC_{inf} - AUC_{\tau})] / AUC_{\tau} - (DOF/2)$ , where $AUMC_{\tau}$ is the area under the moment curve from time 0 until the end of the dosing interval ( $\tau$ ), and DOF is the duration of the IV infusion dose.
$V_z/F^*$ (Cohort 4 only)	Manogepix	Apparent volume of distribution	$\text{Dose}/(AUC_{\tau} \times k_{el})$ .
$C_{\text{trough}}$	Manogepix	Pre-dose concentration	Observed directly from data obtained on Day 7 and Day 8 (24 hours after last dose) <sup>#</sup> .
F	Manogepix	Absolute bioavailability	$AUC_{\tau,po}(\text{dose normalized}) (\text{mean } AUC_{\tau} \text{ in Cohort 4}) / AUC_{\tau,iv}(\text{dose normalized}) (\text{mean } AUC_{\tau} \text{ in Cohort 3})$

\* As data permit.

<sup>#</sup> Other pre-dose concentrations will be collected on Day 1 (second dose), Day 2, Day 3, and Day 6.

If multiple maxima occur at equal concentrations, the first temporal value will be taken for  $T_{\max}$ . The number of data points included in the regression of  $k_{el}$  and  $t_{1/2}$  after single dose will be determined by visual inspection, but a minimum of 3 data points in the terminal phase, excluding  $C_{\max}$ , will be required to estimate  $k_{el}$ . The  $k_{el}$  values (and consequently  $t_{1/2}$ ,  $CL/F$ ,  $V_z/F$ ,  $AUC_{inf}$ ) will be considered unreliable estimates – and therefore excluded from analysis – if the period of time over which an individual  $k_{el}$  was estimated is less than twice the resultant  $t_{1/2}$  or if the adjusted coefficient of determination R-squared is less than or equal to 0.75.

The proportion of  $AUC_{inf}$  due to extrapolation ( $AUC_{extrap}$ ) will also be calculated and expressed as a percentage. The value of  $AUC_{extrap}$  should be less than or equal to 20% for  $AUC_{inf}$  to be considered to be well estimated. If  $AUC_{extrap}$  is higher than 20%, then the values of  $AUC_{inf}$ ,  $CL/F$ ,  $V_z/F$ ,  $t_{1/2}$ , and  $k_{el}$  will be considered unreliable and therefore excluded from the summaries.

All PK parameters will be summarized with descriptive statistics (n, mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV). For  $T_{\max}$ , only n, median, minimum and maximum will be presented. All parameters will be listed, and those

that compromise the reliability of other parameters (e.g.,  $AUC_{extrap}$ ,  $k_{el}$ ) will be marked with an indication.

Box and whisker plots of PK parameters  $C_{max}$ ,  $AUC_{0-24h}$ ,  $AUC_{inf}$ , and  $AUC_{tau}$  will be provided, as applicable. For Part-2, trough concentrations over time will be plotted (mean and SD) for manogepix by study day.

## 9 SAFETY ANALYSIS

All safety analyses will be conducted using the Safety set, unless otherwise specified.

### 9.1 Adverse events

Adverse events are defined in the protocol Appendix 3.

A treatment-emergent AE (TEAE) is defined as any event not present prior to the first administration of the study drug, or any event already present that worsens in either severity or frequency following exposure to the study drug.

An AE that occurs prior to the first administration of the study drug will be considered a non-treatment emergent AE.

An overview summary will be provided for the number and percentage of subjects with any TEAE, serious TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, TEAEs leading to death, TEAEs of special interest. A similar summary will be provided for study drug-related TEAEs.

All TEAEs, non-TEAEs, SAEs, AEs leading to death, and AEs of special interest (AESIs) will be presented in separate listings.

#### 9.1.1 Incidence of adverse events

If appropriate, the number and percentage of subjects reporting AEs will be tabulated by system organ class (SOC) and preferred term (PT) for all TEAEs, and separately for study drug-related TEAEs. Subjects with multiple events will be counted only once within each category. SOC and PT will be sorted in descending order of frequency overall.

#### 9.1.2 Severity of adverse events

Severity of AEs is assessed by the investigator according to CTCAE (version 5.0) as 'Mild' (Grade 1), 'Moderate' (Grade 2), 'Severe' (Grade 3), 'Life-threatening' (Grade 4), or 'Death' (Grade 5). A summary of TEAEs by severity will be presented in a table. If a subject reports multiple occurrences of the same AE, only the most severe will be counted. AEs that are missing severity will be presented in tables as severity 'Unknown'.

#### 9.1.3 Adverse events of special interest

AESIs include neurological reactions, hepatic reactions, testicular findings, and nausea/vomiting.

They will be summarized in a similar manner to that described in Section 9.1.1 for the following AESIs:

- Neurological reactions:
  - AEs reported in the SOC *Nervous system disorders and Psychiatric disorders*
  - AEs identified using Standardized MedDRA Queries (SMQ) such as *Non-infectious encephalopathy/delirium* and *Parkinson-like events*
- Hepatic reactions:
  - AEs reported in the SOC *Hepatic disorders*
  - AEs identified using SMQ such as Liver related investigations, signs and symptoms.
- Testicular findings: AEs identified using SMQ as *Fertility disorders*
- Nausea/Vomiting: AEs identified using MedDRA PTs *Nausea* and *Vomiting*.

#### 9.1.4 Medication errors

Medication errors are reported on a separate form in the eCRF. All medication errors will be listed.

## 9.2 Clinical laboratory evaluations

Local laboratory tests include chemistry, hematology, urinalysis, serology, and drug and alcohol screen parameters in accordance with the protocol Table 9.

Summary tables for laboratory parameters will be generated, including actual values and change from baseline values for clinical laboratory tests with numeric values at baseline and post-baseline scheduled assessments. Additionally, minimum and maximum post-baseline values will be summarized.

Laboratory data will also be summarized using shift tables where appropriate. Each continuous laboratory parameter values will be flagged as “low”, “normal”, or “high” relative to the normal ranges. Each categorical laboratory parameter values will be flagged as “abnormal” or “normal”. These categorical data will be summarized in shift tables comparing value at baseline visit with those at the relevant post-baseline visits, and the minimum and maximum post-baseline values, where appropriate.

Laboratory results will be graded using the CTCAE v5.0. These categorical data will be summarized in shift tables.

Laboratory data collected at unscheduled visits will be included in listings and will contribute to tables of shifts from baseline to minimum and maximum post-baseline.

If any laboratory value falls above or below the upper or lower level of quantification, the following rule will be applied for summary statistics: values reported as <xx or ≤xx will be analyzed as xx/2; values reported as >xx or ≥xx will be analyzed as xx.

Differentials will be displayed in the laboratory output as absolute values.

All clinical laboratory parameters will be presented in listings including normal ranges and indicating if the value is out of range.

### 9.2.1 Potential drug-induced liver injury (Hy's law)

Abnormal elevations in either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) in addition to total bilirubin (TBili), that meet the criteria outlined in the protocol Appendix 5, are considered potential drug-induced liver injury (DILI). Subjects identified with abnormal elevation in one or more of these parameters will be identified and listed.

For the subjects identified, ALT, AST, TBili, as well as albumin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time, international normalized ratio, total bile acids, and alkaline phosphatase will be listed by visit.

### 9.3 Vital signs

Summary tables of observed values and changes from baseline as well as minimum and maximum post-baseline values will be presented for vital sign data, including weight (kg), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C), pulse rate (beats/min), respiratory rate (breaths/minute), and oxygen saturation (%) at baseline and post-baseline scheduled assessments.

### 9.4 Electrocardiogram

Summary tables of observed values, changes from baseline as well as minimum and maximum post-baseline value will be presented for electrocardiogram data, including Heart Rate (bpm), PR Interval (msec), QRS Interval (msec), QT Interval (msec) and QTcF Interval (msec) at each scheduled visit.

The number and percentage of subjects with maximum post-baseline value and maximum change from baseline in the categories shown in Table 3 will be tabulated for QTcF Interval.

**Table 3 Safety QTcF assessment**

	Degree of prolongation (msec)		
Absolute value	> 450 – 480	> 480 – 500	> 500
Increase from baseline		> 30 – 60	> 60

A shift table from baseline to post-baseline ECG interpretations by visit will be displayed.

## 10 INTERIM ANALYSES

No interim analyses will be performed.

## 11 CHANGES IN THE PLANNED ANALYSIS

To harmonize the AESIs across fosmanogepix studies, the list of AESIs and the criteria for their identification have been updated. *Nausea* and *Vomiting* have been added, while

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*Embryofetal toxicity* has been removed. The terms used to identify these AESIs are provided in Section 9.1.3 and are consistent with project reference documents.

## 12 APPENDICES

### Appendix 1 Adverse event date imputations

#### Imputation rules for partial dates

##### *Adverse event start date imputation*

Parameter	Missing	Additional conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y is after Y of first dose	1 January
	D, M, Y	None – date completely missing	Date of first dose of study drug

D = day; M = month; Y = year; AE = adverse event.

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.