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CLINICAL STUDY 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

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DOCUMENT APPROVAL

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Abs	Absolute
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-24h}	Area under the concentration-time curve from time 0 to 24 hours
AUC_{0-t}	Area under the concentration-time curve from 0 to time t
AUC_{inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{last}	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration
AUC_{tau}	Area under the concentration-time curve at steady state over the dosing interval tau
$AUC_{tau,po}$	Area under the concentration-time curve at steady state after oral administration over the dosing interval tau
$AUC_{tau,iv}$	Area under the concentration-time curve at steady state after IV infusion over the dosing interval tau
AUMC	Area under the first moment curve
$AUMC_{inf}$	Area under the first moment curve from time 0 to infinity
AV	Atrioventricular
β-hCG	β-human chorionic gonadotropin
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CL	Total clearance of drug
CL/F	Apparent oral clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CO_2	Carbon dioxide
CO_2CP	Carbon dioxide combining power

CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Pre-dose concentration
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
ECC	Emergency contact card
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOST	End of study treatment
EU	European Union
F	Absolute bioavailability
FSH	Follicle stimulating hormone
f_u	Fraction unbound
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GPI	Glycosylphosphatidylinositol
Gwt1	GPI-anchored cell wall transfer protein 1
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C antibody
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
ID	Identification
IEC	Independent Ethics Committee
IFI	Invasive fungal infection
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous(ly)
k_{el}	First-order elimination rate constant
LFT	Liver function test
MIC	Minimal inhibitory concentration

MRT	Mean residence time
NA	Not applicable
NOAEL	No observed adverse effect level
PD	Pharmacodynamic(s)
PIGW	Phosphatidylinositol Glycan Anchor Biosynthesis Class W
PK	Pharmacokinetic(s)
PPB	Plasma protein binding
PR	Pulse rate
PT	Prothrombin time
PVC	Premature ventricular contraction/complex
QD	Once daily
QTc	Corrected QT
QTcF	QTc corrected using Fridericia's formula
RBC	Red blood cell
RSI	Reference Safety Information
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
spp.	Species
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal phase half-life
TBili	Total bilirubin
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
T_{max}	Time to first occurrence of C_{max}
TPPA	Treponema pallidum particle agglutination assay
ULN	Upper limit of normal
V_{ss}	Steady-state volume of distribution
V_z/F	Apparent volume of distribution for extravascular dosing
WBC	White blood cell
WOCBP	Woman of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

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

Brief title

A Phase 1 study of fosmanogepix in healthy adult Chinese subjects.

Rationale

The purpose of the study is to investigate the pharmacokinetics (PK), safety, and tolerability of fosmanogepix (and manogepix, the active moiety of fosmanogepix) following single and repeated doses (by IV infusion or oral administration) in healthy adult Chinese subjects. The results from this study will support the clinical development of fosmanogepix and a new drug application in China.

Objectives and endpoints

The primary and secondary objectives and endpoints for PART-1 (single-dose part) and PART-2 (multiple-dose part) are presented in Table 1.

Table 1 Synopsis: Objectives and endpoints

Objectives	Endpoints
PART-1 (Single-dose)	
Primary	
To evaluate the PK profile of manogepix (active moiety of fosmanogepix) after single dose administration in healthy adult Chinese subjects.	• Plasma PK parameters for manogepix: – C_{max}, T_{max}, $AUC_{0\text{-}24h}$, AUC_{last}, AUC_{inf} – CL (or CL/F for Cohort 1), V_{ss} (or V_z/F for Cohort 1), $t_{½}$, F as permitted by data
Secondary	
To evaluate the safety and tolerability of fosmanogepix in healthy adult Chinese subjects.	• Incidence of adverse events (AEs) / serious adverse events (SAEs), clinical safety laboratory tests, vital signs, 12-lead ECGs
To evaluate the PK profile of fosmanogepix (pro-drug of manogepix) after single dose administration in healthy adult Chinese subjects.	• Plasma PK parameters for fosmanogepix will be calculated depending on measurable concentrations: – C_{max}, T_{max}, AUC_{last}, and $AUC_{0\text{-}24h}$
To evaluate the plasma protein binding of manogepix (active moiety of fosmanogepix) after single dose administration in healthy adult Chinese subjects.	• Plasma PK parameters for manogepix: – Fraction unbound (f_u)

Objectives	Endpoints
PART-2 (Multiple-dose)	
Primary	
To evaluate the PK profile of manogepix (active moiety of fosmanogepix) after repeated doses in healthy adult Chinese subjects.	• Plasma PK parameters for manogepix: – 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), $t_{½}$, 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
Secondary	
To evaluate the safety and tolerability of fosmanogepix in healthy adult Chinese subjects.	• Incidence of AEs/SAEs, clinical safety laboratory tests, vital signs, 12-lead ECGs
To evaluate the PK profile of fosmanogepix (prodrug of manogepix) after repeated doses in healthy adult Chinese subjects.	• Plasma PK parameters for fosmanogepix will be calculated depending on measurable concentrations: – C_{max}, T_{max}, and AUC_{0-24h} on Day 7

PK parameters are defined in Table 6 and Table 7.
AE = adverse event; ECG = electrocardiogram; PK = pharmacokinetic(s); SAE = serious adverse event.

Overall design

Brief summary

This Phase 1, randomized, single-center, double-blind, placebo-controlled study will investigate the PK, safety and tolerability of fosmanogepix in healthy adult Chinese subjects.

Number of subjects

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.

Inclusion criteria (abbreviated)

(The full list of detailed inclusion criteria is provided in Section 5.1)

Subjects must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Male and female Chinese subjects aged 18 to 65 years, inclusive, at Screening.
2. Body mass index (BMI) of 18.0 to 30.0 kg/m^2 inclusive, and a total body weight > 45 kg for females and > 50 kg for males at Screening.
3. Subjects who are overtly healthy as determined by medical evaluation, including medical history, physical examination, laboratory tests, vital signs, creatinine, and estimated creatinine clearance (Cockcroft-Gault formula).

Exclusion criteria (abbreviated)

(The full list of detailed exclusion criteria is provided in Section 5.2)

Subjects are not eligible to be included in the study if any of the following criteria apply:

2. Active acute or chronic infection, including, but not limited to upper airway infection, urinary tract infection, or skin infection at Screening.
3. Any condition possibly affecting drug absorption (e.g., gastrectomy, cholecystectomy).
6. Medical history of neurological disorders including abnormal movements or seizures.
8. Use of prescription or non-prescription drugs, including vaccines, and dietary and herbal supplements from Screening or within five half-lives (whichever is longer) prior to the first dose of study drug and throughout the study (see Section 6.9 for additional details).
11. Screening supine blood pressure (BP) ≥ 140 mmHg (systolic) or ≥ 90 mmHg (diastolic), and pulse rate (PR) > 100 beats per minute (bpm) or < 50 bpm, following at least 5 minutes of supine rest.
12. Body temperature higher than 37.5 °C.
13. Screening supine 12-lead ECG demonstrating clinically-relevant abnormalities that may affect subject safety or interpretation of study results (e.g., QTcF interval > 450 msec, QRS interval > 120 msec, complete left bundle branch block, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias).
14. Subjects with any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the local laboratory and confirmed by a single repeat test, if deemed necessary:
    - AST or ALT ≥ 1.0 × ULN.
    - Total bilirubin ≥ 1.5 × ULN; subjects with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Treatment groups and duration of treatment and observation

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.

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 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. A minimum of 3 days is required between the last subject being dosed in Cohort 1 and the first subject being dosed in Cohort 2.

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.

Eligible subjects will be admitted to the clinical site on Day −1. The treatment and observation period will comprise admission with baseline assessments on Day −1, an in-clinic stay for 5 days from Day 1 to Day 5, and two outpatient visits on Day 7 and Day 11 (see the Schedule of assessments).

PART-2: Multiple-dose part

PART-2 will only start once PART-1 of the study is completed (excluding Follow-up).

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 BID 12 hours apart on Day 1. In Cohort 3, subjects will receive the maintenance dose via a 3-hour IV infusion, 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.

Eligible subjects will be admitted to the clinical site from Day −1 to completion of Day 11, and will return to the clinical site for outpatient visits on Day 13, Day 17, and Day 22 (see the Schedule of assessments).

Both PART-1 and PART-2

Following the last outpatient PK and safety assessments on Day 11 for PART-1 and Day 22 for PART-2, all subjects will have a follow-up phone call for safety assessment 28 – 35 days after the last dose. This follow-up may be conducted as an on-site visit at the discretion of the Investigator based on the subject's safety profile.

Statistical methods

Sample size

The sample sizes for PART-1 (32 subjects) and PART-2 (20 subjects) are based on the need to minimize the first exposure of healthy adult Chinese subjects to fosmanogepix, and the requirement to obtain adequate PK, safety, and tolerability data at each cohort and dose level.

Analyses

The data from PART-1 and PART-2 of the study will be analyzed and reported separately.

All data analyses will be descriptive. The plasma PK parameters of manogepix and fosmanogepix (if available) will be listed and descriptively summarized by cohort and dose level. For AUCs and C_{max}, box and whisker plots will be plotted for each analyte by cohort and dose level. In PART-2, trough concentrations over time will be plotted for manogepix by study day. For each cohort and dose level, the plasma concentrations of manogepix and fosmanogepix (if available) will be listed and descriptively summarized by study day and nominal PK sampling times. Individual subject and summary profiles (mean and median plots) of the plasma concentration time data will be plotted using actual and nominal sampling times, respectively, for each analyte by cohort and dose level.

Safety data (AEs/serious adverse events [SAEs], ECGs, vital signs, and safety laboratory data) will be presented in tabular and/or graphical format, and summarized descriptively by cohort and dose level, where appropriate.

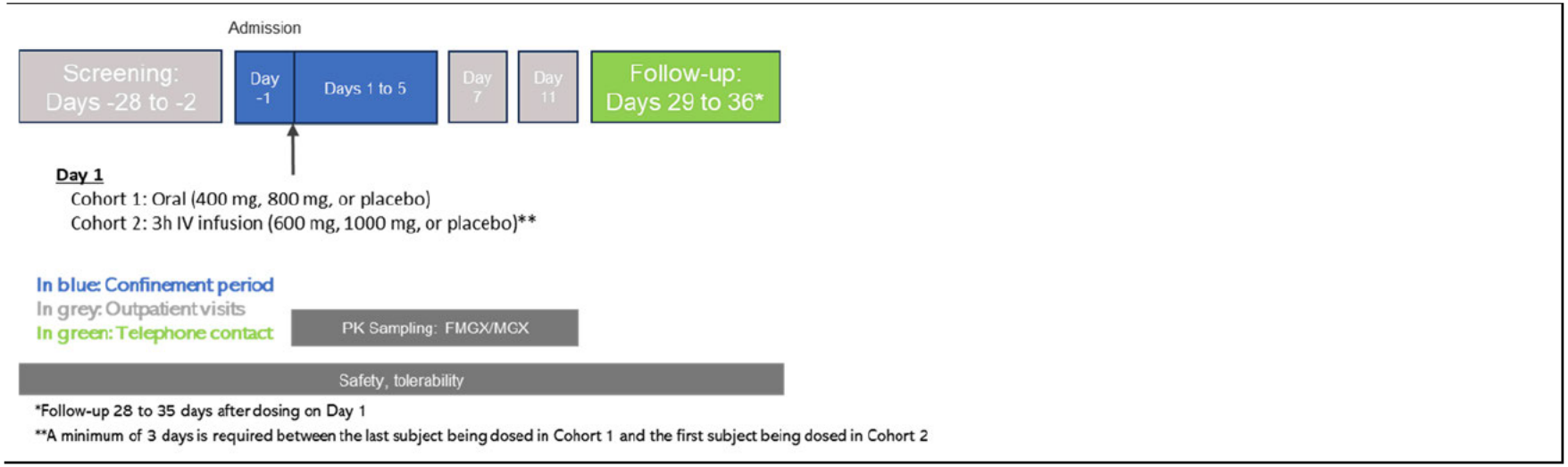
Benefit-risk assessment

Fosmanogepix is not expected to provide any clinical benefit to healthy subjects in this study. Taking into account the measures taken to minimize risk to subjects of this study, the potential risks identified in association with the administration of fosmanogepix are justified by the anticipated benefit, in terms of contribution to the process of developing a new therapy for the Chinese population in an area of unmet medical need.

1.2 Schema

Figure 1 FMGX-CP-109 study design

PART-1: Single-dose (Cohort 1 and Cohort 2)



PART-2: Multiple-dose (Cohort 3 and Cohort 4)

1.3 Schedule of assessments

The Schedule of Assessments provides an overview of the protocol visits and procedures. See Section 8 for detailed information on the requirements for each procedure and assessment. The Investigator may schedule unplanned visits in addition to those listed in the Schedule of Assessments, to conduct evaluations or assessments required to protect the wellbeing of the subject.

PART-1: Single-dose

Visit identifier[a]	**Screening**	**Treatment and observation**						**Follow-up**[b]	**Early termination/ discontinuation**
Days Relative to Day 1	**Day −28 to Day −2**	**Day −1**	**Day 1**	**Day 2–4**	**Day 5**	**Day 7**	**Day 11**	**Day 29 – 36**	
Informed consent	X								
Confinement[c]		→	→	→	→				
Outpatient visit	X					X	X		X
Inclusion/exclusion criteria	X	X							
Medical history[d]	X								
Physical examination[e]	X	X					X		X
Height and weight[f]	X	X					X		X
Safety laboratory tests[g]	X	X	X				X		X
Demography	X								
Pregnancy test (WOCBP only)[h]	X	X					X		X
Contraception check[i]	X	X			X			X	X
FSH[j]	X								
Urine drug testing / alcohol testing[k]	X	X							
12-Lead ECG[l]	X		X				X		X
Vital signs (BP, PR, temperature, respiratory rate, oxygen saturation) [l]	X		X				X		X
HIV, HBsAg, HCVAb, HBcAb, TPPA	X								
Prior and concomitant medications	X	X	X	X	X	X	X	X	X
Study drug administration[m]			X						
PK blood sampling[n]			X	X	X	X	X		
Blood sampling for PPB[o]			X						
Discharge					X				
AE monitoring	X	→	→	→	→	→	→	X	X

For abbreviations see the List of Abbreviations above.
For footnotes, see next page.

a. Day relative to study drug dosing (Day 1).
b. Follow-up is to be by telephone contact 28 to 35 days (Day 29 to Day 36) after administration of study drug.
c. The subject is permitted to leave the clinical site on Day 5 in the morning. The confinement period may be extended at the Investigator's discretion, for safety or logistical reasons.
d. Medical history will include a history of prior illegal drug, alcohol, and tobacco use, as well as blood donation within prior 60 days. Medical history will be recorded at Screening; any event occurring after ICF has been signed will be recorded as AE.
e. A complete physical examination must be performed by trained medical personnel at Screening, and a brief physical examination must be performed at all the other time points (see Section 8.2.1).
f. Height is to be measured at Screening only to obtain BMI.
g. Blood for safety laboratory tests (hematology, clinical chemistry, and urinalysis) should be taken after at least 4 hours of fasting during Screening and on Day −1, on Day 11, and at Early discontinuation, if applicable. On Day 1, blood for safety laboratory tests should be taken at 3 hours (±30 minutes) after dose administration/start of infusion. Additional safety laboratory assessments may be performed at any time at the discretion of the Investigator.
h. Pregnancy tests (urine or serum) are to be performed for women of childbearing potential only (see Section 8.2.5).
i. The Investigator must discuss with the subject the need to use highly effective contraception consistently and correctly in accordance with the contraception guidelines (see Section 5.3.4 and Appendix 4).
j. For postmenopausal (amenorrheic for at least 12 consecutive months) female subjects only.
k. Urine drug test may be performed at any other time at the discretion of the Investigator.
l. 12-lead ECGs and vital signs should be conducted during Screening, on Day 1 prior to dosing in the morning (within 2 hours of study drug administration), on Day 11, and at Early discontinuation, if applicable. All ECG assessments and vital signs tests are to be made after at least a 5-minute rest in a supine position. The order is ECG assessment before vital signs and before any blood draws. Additional ECGs and vital signs (BP, PR, temperature, respiratory rate, and oxygen saturation) may be performed at any time at the Investigator's discretion.
m. All subjects in PART-1 receive a single dose administration on Day 1 after 10 hours fasting. In Cohort 1, subjects will receive study drug by oral administration. In Cohort 2, subjects will receive study drug by 3-hour IV infusion.
n. Blood samples for PK analysis will be taken at each time point. See the PK Sampling Schedule below.
o. Blood samples for PPB analysis will be taken on Day 1 pre-dose, and 3 hours post-dose. See the PK Sampling Schedule below.

PART-1: PK sampling schedule

Study day	**Day 1**								**Day 2**		**Day 3**	**Day 4**	**Day 5**	**Day 7**	**Day 11**
Hours after dose[a] (±PK sampling window)	**0[b]**	**1** (±6 min)	**2** (±12 min)	**3[c]**	**4** (±24 min)	**6** (±30 min)	**8** (±30 min)	**12** (±1 h)	**24** (±1 h)	**36** (±1 h)	**48** (±1 h)	**72** (±1 h)	**96** (±1 h)	**144** (±3 h)	**240** (±3 h)
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for PPB	X			X											

For abbreviations see the List of Abbreviations above.

a. The PK collection time points are shown in hours relative to the start of single dose administration on Day 1.

b. Pre-dose sample collection, 30 minutes before single dose administration (start time) on Day 1. The blood samples should be taken after at least 10 hours of fasting.

c. For Cohort 1, the PK and PPB samples should be collected within ±18 minutes after the 3-hour oral administration time point. For Cohort 2, the PK and PPB samples should be collected within 5 minutes before the end of infusion.

PART-2: Multiple-dose

Visit identifier[a]	Screening	Treatment and observation												Follow-Up[b]	Early termination/ discontinuation
Days Relative to Day 1	**Day −28 to Day −2**	**Day −1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8 – 11**	**Day 13**	**Day 17**	**Day 22**	**Day 35 – 42**	
Informed consent	X														
Confinement[c]		→	→	→	→	→	→	→	→	→					
Outpatient visit	X										X	X	X		X
Inclusion/exclusion criteria	X	X													
Medical history[d]	X														
Physical examination[e]	X	X											X		X
Height and weight[f]	X	X											X		X
Safety laboratory tests[g]	X	X	X			X			X				X		X
Demography	X														
Pregnancy test (WOCBP only)[h]	X	X											X		X
Contraception check[i]	X	X								X				X	X
FSH[j]	X														
Urine drug testing / alcohol testing[k]	X	X													
12-Lead ECG[l]	X		X			X			X				X		X
Vital signs (BP, PR, temperature, respiratory rate, oxygen saturation)[l]	X		X			X			X				X		X
HIV, HBsAg, HCVAb, HBcAb, TPPA	X														
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration[m]			X	X	X	X	X	X	X						
PK blood sampling[n]			X	X	X			X	X	X	X	X	X		X
Discharge										X					
AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	X	X

For abbreviations see the List of Abbreviations above.
For footnotes, see next page.

a. Day relative to start of study drug (Day 1).
b. Follow-up is to be by telephone contact 28 to 35 days (Day 35 to Day 42) after administration of the final dose of study drug.
c. The subject is permitted to leave the clinical site on Day 11 in the morning. The confinement period may be extended at the Investigator's discretion, for safety or logistical reasons.
d. Medical history will include a history of prior illegal drug, alcohol, and tobacco use, as well as blood donation within prior 60 days. Medical history will be recorded at Screening; any event occurring after ICF has been signed will be recorded as AE.
e A complete physical examination must be performed by trained medical personnel at Screening, and a brief physical examination must be performed at all the other time points (see Section 8.2.1).
f. Height is to be measured at Screening only to obtain BMI.
g. Blood for safety laboratory tests (hematology, clinical chemistry, and urinalysis) should be taken after at least 4 hours of fasting during Screening, Day −1, pre-dose (within 30 minutes before study drug administration) on Day 7, on the last observation day (Day 22) morning, and at Early discontinuation, if applicable. On Day 1 and Day 4, blood for safety laboratory tests should be taken at 3 hours (±30 minutes) after dose administration/start of infusion in the morning, without fasting. Additional safety laboratory assessments may be performed at any time at the discretion of the Investigator.
h. Pregnancy tests (urine or serum) are to be performed for women of childbearing potential only (see Section 8.2.5).
i. The Investigator must discuss with the subject at Screening, Day −1, Day 11 (before discharge), and at Follow-up, the need to use highly effective contraception consistently and correctly in accordance with the contraception guidelines (see Section 5.3.4 and Appendix 4).
j. For postmenopausal (amenorrheic for at least 12 consecutive months) female subjects only.
k. Urine drug test may be performed at any other time at the discretion of the Investigator.
l. 12-lead ECGs and vital signs should be conducted during Screening, on Day 1 prior to dosing in the morning (within 2 hours of study drug administration), pre-dose on Day 4 and Day 7, at 3 hours (±30 minutes) after dose administration/start of infusion on Day 4, in the morning on Day 22, and at Early discontinuation, if applicable. All ECG assessments and vital signs tests are to be made after at least a 5-minute rest in a supine position. The order is ECG assessment before vital signs and before any blood draws. Additional ECGs and vital signs (BP, PR, temperature, respiratory rate, oxygen saturation) may be performed at any time at the Investigator's discretion.
m. All subjects in PART-2 receive a loading dose of 1,000 mg fosmonagepix or placebo (3-hour IV infusion, BID) on Day 1 after 4 hours fasting followed by a maintenance dose of 600 mg or placebo (3-hour IV infusion, QD) on Days 2 and 3. Subjects in Cohort 3 will then continue to receive the IV maintenance dose administration of 600 mg fosmanogepix or placebo, QD. Subjects in Cohort 4 will switch to oral administration of 800 mg fosmanogepix or placebo, QD on Days 4 – 7. On Day 7, all subjects (Cohort 3 and Cohort 4) will receive study drug after 10 hours fasting.
n. Blood samples for PK analysis will be taken at each time point. See the PK Sampling Schedule below.

PART-2: PK sampling schedule

Study day	**Day 1**			**Day 2, 3, 6**	**Day 7**								**Day 8**		**Day 9**	**Day 10**	**Day 11**	**Day 13**	**Day 17**	**Day 22**
Hours after dose[a] (±PK sampling window)	**0[b]**	**3[d] (End of first dose on Day 1)**	**12[c] (Pre-dose of second dose on Day 1)**	**0[c]**	**0[c]**	**1** (±6 min)	**2** (±12 min)	**3[d]**	**4** (±24 min)	**6** (±30 min)	**8** (±30 min)	**12** (±1 h)	**24** (±1 h)	**36** (±1 h)	**48** (±1 h)	**72** (±1 h)	**96** (±1 h)	**144** (±3 h)	**240** (±3 h)	**360** (±3 h)
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

For abbreviations see the List of Abbreviations above.

a. The PK collection time points on Day 1 are shown in hours relative to the start of first dose administration on Day 1. The PK collection time points from Day 7 to Day 22 are shown in hours relative to the start of the last dose on Day 7. On Day 7, the PK sample should be taken after at least 10 hours of fasting.

b. Pre-dose PK sample collection, 30 minutes before first dose administration (start time) on Day 1. The PK sample should be taken after at least 10 hours of fasting.

c. Pre-dose PK sample collection, 30 minutes before second dose administration (start time) on Day 1, and before administration (start time) on Day 2, Day 3, Day 6, and Day 7.

d. The PK sample should be collected within 5 minutes before the end of infusion (for all subjects on Day 1, and for Cohort 3 only on Day 7). For Cohort 4 on Day 7, the PK sample should be collected 3 hours (±18 minutes) after administration of the oral dose.

2 INTRODUCTION

Fosmanogepix (previously PF-07842805 or APX001) is a novel first-in-class small molecule fungal Gwt1 inhibitor being investigated as an IV/oral treatment in invasive fungal infections (IFIs). Fosmanogepix is a water-soluble phosphate prodrug which is rapidly and completely metabolized to the active moiety manogepix (previously PF-07843326 or APX001A).

Fosmanogepix has a novel mechanism of antifungal action with broad spectrum *in vitro* activity against major fungal pathogens including *Candida*, *Cryptococcus*, *Aspergillus*, *Scedosporium*, *Fusarium*, and members of the Mucorales order (Castanheira 2012, Pfaller 2011a, Pfaller 2011b, Huband 2019).

2.1 Study rationale

The purpose of the study is to investigate the PK, safety, and tolerability of fosmanogepix (and manogepix, the active moiety of fosmanogepix) following a single dose and repeated doses (by IV infusion or oral administration) in healthy adult Chinese subjects. The results from this study will support the clinical development of fosmanogepix and a new drug application in China.

2.2 Background

Fosmanogepix has the potential to provide a much-needed treatment alternative for systemic *Candida* infections, including multi-drug resistant and intrinsically-resistant strains associated with high mortality. Other differentiating factors vs existing classes of antifungals include a low potential for CYP3A4 inhibition, wide tissue distribution (including central nervous system [CNS]/eye), and the advantage of both IV and oral formulations, allowing for a continuation of care outside of the hospital.

Manogepix inhibits the conserved fungal enzyme Gwt1, which is required for the expression of GPI-anchored proteins on the fungal cell wall. Inhibition of Gwt1 by manogepix compromises cell wall integrity, inhibits biofilm formation, blocks filamentation, enhances immunogenicity of unmasked β-glucan, and produces severe fungal growth defects (Watanabe 2012, McLellan 2012). The closest mammalian ortholog of Gwt1 is PIGW, which has no demonstrable inhibition by manogepix.

Manogepix has demonstrated broad *in vitro* antifungal activity against *Candida* spp., including activity against azole-resistant and echinocandin-resistant strains (Hata 2011). Manogepix has demonstrated synergy with echinocandins (*Aspergillus*) (Wiederhold 2015) and azoles (*Candida*) (Hata 2011). In invasive fungal disease animal models, including those for *Aspergillus* and *Candida* that are resistant to azoles, manogepix has demonstrated high survival rates and reduced colony counts of fungi in the lungs of infected mice (Hata 2011, Wiederhold 2015). The PK/PD driver that best correlated with efficacy was AUC/MIC (Zhao 2018).

Eight Phase 1 clinical studies of fosmanogepix have evaluated the safety, tolerability, and PK of single and multiple-ascending doses administered IV and orally. Seven Phase 1 studies were conducted in healthy subjects, and one study (APX001-103) was conducted

in subjects with acute myeloid leukemia (AML), in which 261 subjects received at least one dose of fosmanogepix.

Three open-label, non-comparative Phase 2 studies have been completed. In a Phase 2 proof-of-concept study for the treatment of candidemia (APX001-201), 21 subjects were treated with fosmanogepix for up to 14 days (IV with an optional switch to oral). In an open-label study for the treatment of candidemia and/or invasive candidiasis caused by *Candida auris* (APX001-203), nine subjects were treated with fosmanogepix for up to 42 days (IV with an optional switch to oral). In an open-label study for the treatment of invasive mold infections caused by *Aspergillus* species or rare molds in patients with limited antifungal treatment options (APX001-202), 21 subjects were treated with fosmanogepix for up to 42 days (IV with an optional switch to oral).

2.2.1 Nonclinical overview

[redacted]

[redacted]

Additional nonclinical information for fosmanogepix is provided in the fosmanogepix Investigator's Brochure (IB).

2.2.2 Clinical overview

2.2.2.1 Phase 1 studies in healthy subjects

[redacted]

[redacted]

2.2.2.2 Phase 1b study in subjects undergoing chemotherapy for AML

[redacted]

2.2.2.3 Phase 2a proof-of-concept study in the treatment of candidemia

[redacted]

2.2.2.4 Phase 2a proof-of-concept study in the treatment of candidemia and/or invasive candidiasis caused by *Candida auris*

[redacted]

2.2.2.5 Phase 2 study in the treatment of invasive mold infections caused by *Aspergillus* spp. or rare molds

[redacted]

Further details on the safety, clinical results, and PK of fosmanogepix, including results from the above studies, are presented in the latest version of fosmanogepix IB.

2.2.2.6 Expanded Access Program

[redacted] Expanded Access Program (EAP) (NCT06433128).

2.2.2.7 Phase 3 study in the treatment of candidemia and/or invasive candidiasis

Study FMGX-CS-301 is a global, multicenter, randomized, active-controlled, double-blind Phase 3 study and investigates fosmanogepix IV versus a standard-of-care regimen of

caspofungin IV in adult patients with candidemia and/or invasive candidiasis. The study is expected to enroll approximately 450 patients, who will be randomized in a 2:1 ratio to either fosmanogepix or caspofungin. There is an optional oral switch to fosmanogepix in the fosmanogepix group and to fluconazole in the caspofungin group. As of September 2024, this study is open for enrollment.

2.3 Benefit/risk assessment

Fosmanogepix is not expected to provide any clinical benefit to healthy subjects. This study is designed primarily to generate PK, safety and tolerability data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of fosmanogepix may be found in the fosmanogepix IB, Section 6 of which is the Reference Safety Information (RSI) for this study.

The risk assessment for the study is presented in Table 2.

Table 2 Risk assessment for fosmanogepix

Potential risks of clinical significance	Rationale	Mitigation strategy
Central nervous system toxicity	The potential risk is based on nonclinical toxicology findings and isolated cases in humans.	Eligibility criteria have been selected to ensure that only appropriate subjects are included in the study, and study procedures are in place to evaluate this risk, i.e., physical examination (see Section 8.2.1).
Liver toxicity	The potential risk is based on nonclinical toxicology findings and on liver enzyme elevations observed in early clinical studies. No subjects met the criteria for DILI in these studies.	Eligibility criteria have been selected to exclude subjects with hepatic impairment and/or raised liver enzymes/bilirubin. AEs and clinical laboratory results will be monitored on an ongoing basis, and instructions for managing potential cases of DILI are provided in Appendix 5.
Testicular toxicity	The potential risk is based on nonclinical toxicology findings in a single species at exposure levels ~1 – 2 times that expected with the clinical dose regimen. Animal experiments did not permit a conclusion of full reversibility of testicular toxicity.	Male subjects are informed of the potential risk of testicular toxicity and impaired fertility before being asked to provide informed consent to participation in the study.
Embryofetal toxicity	Malformations in fetal rats and rabbits have been observed in embryofetal development studies. Occupational hazard assessments have also been performed for fosmanogepix in relation to the reproductive and developmental effects observed in nonclinical studies. These assessments have indicated: • Dermal absorption is the main route of unintentional exposure to fosmanogepix. • There is a minimal risk to health following workplace air exposure under normal and exaggerated conditions of use in healthcare settings.	Pregnant or breastfeeding women are excluded from fosmanogepix clinical studies. Guidance that women of childbearing potential must agree to use highly effective forms of contraception during treatment and observation. To mitigate the risk of dermal absorption of fosmanogepix among pharmacists, this clinical study protocol and the Pharmacy Manual include guidance regarding the preparation of intravenous solutions in a pharmacy or equivalent dedicated space for drug preparation, following clinical site procedures to minimize microbial contamination, and wearing gloves, masks, and gowns. For handling fosmanogepix tablets for oral administration, gloves should be worn. For both formulations, surfaces should be cleaned before and after handling fosmanogepix.

2.3.1 Benefit assessment

Fosmanogepix will not provide any clinical benefit to healthy subjects in this study. Any anticipated benefit to subjects would be in terms of contribution to the process of developing a new therapy in an area of unmet medical need.

2.3.2 Overall benefit/risk conclusion

Fosmanogepix is not expected to provide any clinical benefit to healthy subjects in this study. Taking into account the measures taken to minimize risk to subjects of this study, the potential risks identified in association with the administration of fosmanogepix are justified by the anticipated benefit, in terms of contribution to the process of developing a new therapy for the Chinese population in an area of unmet medical need.

3 OBJECTIVES AND ENDPOINTS

The primary and secondary objectives and endpoints for PART-1 (single-dose part) and PART-2 (multiple-dose part) are presented in Table 3.

Table 3 Objectives and endpoints

Objectives	Endpoints
PART-1 (Single-dose)	
Primary	
To evaluate the PK profile of manogepix (active moiety of fosmanogepix) after single dose administration in healthy adult Chinese subjects.	• Plasma PK parameters for manogepix: – C_{max}, T_{max}, $AUC_{0\text{-}24h}$, AUC_{last}, AUC_{inf} – CL (or CL/F for Cohort 1), V_{ss} (or V_z/F for Cohort 1), $t_{½}$, F as permitted by data
Secondary	
To evaluate the safety and tolerability of fosmanogepix in healthy adult Chinese subjects.	• Incidence of adverse events (AEs) / serious adverse events (SAEs), clinical safety laboratory tests, vital signs, 12-lead ECGs
To evaluate the PK profile of fosmanogepix (pro-drug of manogepix) after single dose administration in healthy adult Chinese subjects.	• Plasma PK parameters for fosmanogepix will be calculated depending on measurable concentrations: – C_{max}, T_{max}, AUC_{last}, and $AUC_{0\text{-}24h}$
To evaluate the plasma protein binding of manogepix (active moiety of fosmanogepix) after single dose administration in healthy adult Chinese subjects.	• Plasma PK parameters for manogepix: – Fraction unbound (f_u)

Objectives	Endpoints
PART-2 (Multiple-dose)	
Primary	
To evaluate the PK profile of manogepix (active moiety of fosmanogepix) after repeated doses in healthy adult Chinese subjects.	• Plasma PK parameters for manogepix: – 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), $t_{½}$, 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
Secondary	
To evaluate the safety and tolerability of fosmanogepix in healthy adult Chinese subjects.	• Incidence of AEs/SAEs, clinical safety laboratory tests, vital signs, 12-lead ECGs
To evaluate the PK profile of fosmanogepix (prodrug of manogepix) after repeated doses in healthy adult Chinese subjects.	• Plasma PK parameters for fosmanogepix will be calculated depending on measurable concentrations: – C_{max}, T_{max}, and AUC_{0-24h} on Day 7

PK parameters are defined in Table 6 and Table 7.
AE = adverse event; ECG = electrocardiogram; PK = pharmacokinetic(s); SAE = serious adverse event.

4 STUDY DESIGN

4.1 Overall 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.

4.1.1 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 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. A minimum of 3 days is required between last subject being dosed in Cohort 1 and first subject being dosed in Cohort 2.

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.

Eligible subjects will be admitted to the clinical site on Day −1. The treatment and observation period will comprise admission with baseline assessments on Day −1, an in-clinic stay for 5 days from Day 1 to Day 5, and two outpatient visits on Day 7 and Day 11 (see the Schedule of assessments).

4.1.2 PART-2: Multiple-dose part

PART-2 will only start once PART-1 of the study is completed (excluding Follow-up).

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 BID 12 hours apart on Day 1. In Cohort 3, subjects will receive the maintenance dose via a 3-hour IV infusion, 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.

Eligible subjects will be admitted to the clinical site from Day −1 to completion of Day 11, and will return to the clinical site for outpatient visits on Day 13, Day 17, and Day 22 (see the Schedule of assessments).

4.1.3 Both PART-1 and PART-2

Following the last outpatient PK and safety assessments on Day 11 for PART-1 and Day 22 for PART-2, all subjects will have a follow-up phone call for safety assessment 28 – 35 days after the last dose. This follow-up may be conducted as an on-site visit at the discretion of the Investigator based on the subject's safety profile.

4.1.4 Replacement of subjects

A subject who discontinues prior to the completion of the study (Day 11 and Day 22 for PART-1 and PART-2, respectively) may be replaced at the discretion of the Investigator and Sponsor.

4.2 Scientific rationale for study design

The purpose of the study is to investigate the pharmacokinetics, safety and tolerability of manogepix and fosmanogepix following single and repeated IV and oral doses in healthy adult Chinese subjects. The results from this study will support the clinical development of fosmanogepix and a new drug application in China.

4.2.1 Choice of contraception requirements

As nonclinical studies of fosmanogepix suggest a risk of severe manifestations of developmental toxicity at relevant clinical exposures, the use of a highly effective method of contraception is required for women of childbearing potential (see Appendix 4).

4.3 Justification for dose

4.3.1 PART-1: Single-dose part

The single-dose escalation part of the study comprises several dose levels of fosmanogepix following both IV and oral dose administration and selected based on previous Phase 1 studies conducted in non-Chinese populations. The data will be used to support a comprehensive PK comparison between Chinese and non-Chinese populations. In PART-1, Cohort 1 (oral administration) and Cohort 2 (IV infusion) include two dose levels (low, high) to ensure that the dose regimen selected is expected to be safe and well-tolerated.

For oral administration, fosmanogepix shows linear PK characteristics and a favorable safety profile in completed Phase 1 studies after single-oral dose administration from 100 mg to 1,000 mg. The dose of 400 mg oral administration was chosen as the low-dose level of the single dose part since the full completed PK profile in the non-Chinese population is available for that dose. The high dose of 800 mg was chosen to match the planned maintenance oral dose in the multiple dose regimen.

For IV infusion, fosmanogepix also shows linear PK characteristic and a favorable safety profile in completed Phase 1 studies after single-dose administration by IV infusion of doses from 10 mg to 1,000 mg. The low and high dose levels of 600 mg and 1,000 mg IV infusion were chosen to match the planned maintenance and loading doses in the multiple dose regimen based on completed Phase 2 studies.

4.3.2 PART-2: Multiple-dose part

In the Phase 2 proof-of-concept study of fosmanogepix treatment for candidemia (study APX001-201), all 21 subjects received two loading doses of 1,000 mg IV by 3-hour infusion (approximately 12 hours apart), followed by the maintenance dose of 600 mg IV by 3-hour infusion QD from Day 2 until Day 14 (if remaining on IV). Ten of 21 subjects (47%) were switched to oral fosmanogepix at 700 mg QD, and both the IV and oral regimens were demonstrated to be safe and well tolerated.

In the Phase 2 open-label single-arm study APX001-202, for the treatment of invasive mold infections caused by *Aspergillus* spp. or rare molds, 21 patients with documented/anticipated resistance, contraindication, intolerance, or lack of clinical response to standard antifungal therapy received fosmanogepix for up to 42 days. The dosing schedule was Day 1: 1,000 mg BID IV loading dose; Days 2-42: 600 mg QD IV, with optional switch to 800 mg QD oral from Day 4 onwards. Eighteen subjects completed treatment. In total, 258 AEs were reported (n=21); 13 patients had SAEs. Fifteen patients experienced 36 fosmanogepix-related AEs, of whom two had three SAEs. Three patients discontinued study treatment due to fosmanogepix-related AEs.

In Phase 1 studies conducted in non-Chinese healthy subjects investigating fosmanogepix at the clinical dose and regimen used in this study (1,000 mg IV 3-hour infusion BID loading dose, followed by 600 mg IV 3-hour infusion QD or 800 mg oral QD maintenance dose), fosmanogepix was safe and well tolerated.

As this dosing regimen will be used in subsequent planned Phase 3 pivotal studies, the same dosing regimen is appropriate for PART-2 of this study, to allow appropriate comparisons with PK and safety and tolerability data in non-Chinese populations, and to support a New Drug Application for fosmanogepix in China.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last subject in the study (see the Schedule of assessments).

5 STUDY POPULATION

The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this study.

Prospective approval of protocol deviations from these enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Male and female Chinese subjects aged 18 to 65 years, inclusive, at Screening.
2. Body mass index of 18.0 to 30.0 kg/m^2 inclusive, and a total body weight > 45 kg for females and > 50 kg for males at Screening.
3. Subjects who are overtly healthy as determined by medical evaluation, including medical history, physical examination, laboratory tests, vital signs, creatinine and estimated creatinine clearance (Cockcroft-Gault formula).
4. Subjects who are willing and able to comply with all requirements of the study, including confinement periods and ambulatory visits, all study-related procedures, treatment and observation plans, laboratory tests, lifestyle considerations, and other study procedures.
5. Willing and able to give signed informed consent as described in Appendix 1, including compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion criteria

Subjects are not eligible to be included in the study if any of the following criteria apply:

Medical conditions

1. Evidence or history of clinically-significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, diarrhea, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).
2. Active acute or chronic infection, including, but not limited to upper airway infection, urinary tract infection, or skin infection, at Screening.

3. Any condition possibly affecting drug absorption (e.g., gastrectomy, cholecystectomy).
4. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb, HCVAb and TPPA. Note: Hepatitis B vaccination is allowed.
5. Female subject is pregnant or lactating.
6. Medical history of neurological disorders including abnormal movements or seizures.
7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior, or laboratory abnormality that may increase the risk of study participation or, in the Investigator's judgment, make the subject inappropriate for the study.

Prior/concomitant therapy

8. Use of prescription or non-prescription drugs, including vaccines, and dietary and herbal supplements from Screening or within five half-lives (whichever is longer) prior to the first dose of study drug and throughout the study (see Section 6.9 for additional details).

Prior/concurrent clinical study experience

9. Previous administration with an investigational drug within 60 days (or as determined by the local requirement) or five half-lives (whichever is longer) preceding the first dose of study drug.

Diagnostic assessments

10. A positive urine drug test or a positive breath or urine alcohol test.
11. Screening supine blood pressure (BP) $\geq$ 140 mmHg (systolic) or $\geq$ 90 mmHg (diastolic), and pulse rate (PR) > 100 beats per minute (bpm) or < 50 bpm, following at least 5 minutes of supine rest.
12. Body temperature higher than 37.5 °C.
13. Screening supine 12-lead ECG demonstrating clinically-relevant abnormalities that may affect subject safety or interpretation of study results (e.g., QTcF interval > 450 msec, QRS interval > 120 msec, complete left bundle branch block, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias).
14. Subjects with any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the local laboratory and confirmed by a single repeat test, if deemed necessary:
    - AST or ALT $\geq$ 1.0 × ULN
    - Total bilirubin $\geq$ 1.5 × ULN; subjects with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is $\leq$ ULN.

Other exclusions

15. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of ≥ five (for males) or ≥ four (for females) units of alcoholic drinks in 2 hours. Alcohol abuse is defined as alcohol intake exceeding 14 units per week, where 1 unit = 240 mL of beer, 30 mL of 40% spirit, or 90 mL of wine.
16. Blood donation (excluding plasma donations) of approximately 500 mL or more within 60 days prior to first dosing and until the follow-up contact.
17. Use of tobacco or nicotine-containing products in excess of the equivalents of five cigarettes per day or two chews of tobacco per day.
18. History of sensitivity to heparin or heparin-induced thrombocytopenia.
19. Unwilling or unable to comply with the criteria in Section 5.3 Lifestyle considerations.
20. Investigator site staff or Sponsor employees directly involved in the conduct of the study, site staff otherwise supervised by the Investigator, or their respective family members.

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to safety laboratory evaluations, except on Day 1 in PART-1 and Day 7 in PART-2 in which they must abstain at least 10 hours prior to the collection of the pre-dose PK sample. In addition, on Day 1 and Day 4 in PART-2, subjects will not be required to be fasted prior to the safety laboratory evaluations.
- On Day 1 in PART-1 and Day 7 in PART-2, fasting is required for at least 4 hours after starting study drug administration.
- Water is permitted until 1 hour prior to study drug administration (except water used to swallow oral doses). Water may be consumed without restriction beginning 1 hour after oral dosing on Day 1 in PART-1 and Day 7 in PART-2. Water may be consumed without restriction after other doses. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices, see below) may be consumed with meals and the evening snack.
- An evening snack is permitted.
- Subjects must refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (e.g., Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study drug until after collection of the final PK blood sample.
- While subjects are confined in the clinical site, all meals are to be provided by the clinical site as standard meals.

5.3.2 Caffeine, alcohol, and tobacco

- Subjects must abstain from caffeine-containing products for 24 hours prior to the first dose of study drug until after collection of the final PK blood sample.
- Subjects must abstain from alcohol from 24 hours prior (or as specified above for red wine) to admission to the clinical site until after collection of the final PK sample.
- Subjects must abstain from the use of tobacco- or nicotine-containing products from 24 hours prior to the first dose of study drug until the end of confinement(s) in the clinical site.

5.3.3 Activity

- Subjects must abstain from strenuous exercise (e.g., heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace is permitted.
- To standardize the conditions on PK sampling days, subjects will be required to maintain daily activities (such as sitting or walking at a normal pace, except when required for BP, PR, and ECG measurements).

5.3.4 Contraception

The Investigator or his or her designee, in consultation with the subject, must confirm that the subject has selected an appropriate method of contraception from the permitted list of contraception methods (see Appendix 4), and has been instructed in its consistent and correct use. At time points indicated in the Schedule of assessments, the Investigator or designee must inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least one of the selected highly effective methods of contraception) considering that their risk of pregnancy may have changed since the last visit. In addition, the Investigator or designee must instruct the subject to contact the clinical site immediately if the selected contraception method is discontinued, or if pregnancy is known or suspected in the subject or partner.

5.4 Screen failures

Screen failures are defined as subjects who provide consent but are either not considered eligible for the study, or are selected but do not enroll in the study. A minimal set of screen failure information will be collected in the eCRF: demography, screen failure details, eligibility criteria, and any AE.

Subjects who are screen failures may be rescreened with Sponsor approval. In cases where rescreening is permitted, all screening procedures must be repeated. Rescreened subjects should be assigned a new subject number as compared to the initial screening.

6 STUDY DRUG AND CONCOMITANT THERAPY

For the purposes of this protocol, study drug refers to fosmanogepix or placebo.

6.1 Study drug administration

Details of study drug administration will be provided to the site in the Pharmacy Manual. Intravenous drug is to be administered on the contralateral arm from PK sampling.

Table 4 Study drug administration

Study drug name	Fosmanogepix (IV)	Placebo (IV)	Fosmanogepix (oral)	Placebo (oral)
Route of administration	IV infusion	IV infusion	Oral	Oral
Dose formulation	Concentrate for solution for infusion	Solution for infusion	Tablet	Tablet
Unit dose strength(s)	350 mg as a 20 mg/mL solution	0 mg	400 mg	0 mg
Dosage level(s)	See Section 6.1.1 for detailed dosage levels			
Sourcing	Provided centrally by the Sponsor.	Provided locally by the clinical site.	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.
Packaging and labeling	Study drug will be provided in single-use vials with open labels as required per country requirements.	Placebo will be provided by the clinical site in commercial IV bags.	Study drug will be provided in bottles with blinded labels as required per country requirements.	Placebo will be provided in bottles with blinded labels as required per country requirements.
Former names or aliases	PF-07842805/ APX001	NA	PF-07842805/ APX001	NA

IV = intravenous; NA = not applicable.
See the Pharmacy Manual for additional details.

Table 5 Overview of study arms

PART-1: Single-dose			
Arm	**Cohort 1: Fosmanogepix oral (low dose)**	**Cohort 1: Fosmanogepix oral (high dose)**	**Cohort 1: Placebo oral**
Arm description	Single dose of 400 mg fosmanogepix orally on Day 1.	Single dose of 800 mg fosmanogepix orally on Day 1.	Single dose of placebo orally on Day 1.
Arm	**Cohort 2: Fosmanogepix IV (low dose)**	**Cohort 2: Fosmanogepix IV (high dose)**	**Cohort 2: Placebo IV**
Arm description	Single dose of 600 mg fosmanogepix via 3-hour IV infusion on Day 1.	Single dose of 1,000 mg fosmanogepix via 3-hour IV infusion on Day 1.	Single dose of placebo via a 3-hour IV infusion on Day 1.

PART-2: Multiple-dose				
Arm	**Cohort 3: Fosmanogepix IV maintenance dose**	**Cohort 3: Placebo IV maintenance dose**	**Cohort 4: Fosmanogepix oral maintenance dose**	**Cohort 4: Placebo oral maintenance dose**
Arm description	**Loading IV dose:** Fosmanogepix 1,000 mg BID (12 hours apart) via 3-hour IV infusion on Day 1.	**Loading IV dose:** Placebo BID (12 hours apart) via 3-hour IV infusion on Day 1.	**Loading IV dose:** Fosmanogepix 1,000 mg BID (12 hours apart) via 3-hour IV infusion on Day 1.	**Loading IV dose:** Placebo BID (12 hours apart) via 3-hour IV infusion on Day 1.
	Maintenance IV dose: Fosmanogepix 600 mg QD via 3-hour IV infusion on Day 2 to Day 7.	**Maintenance IV dose:** Placebo QD via 3-hour IV infusion on Day 2 to Day 7.	**Maintenance oral dose:** Fosmanogepix 600 mg QD via 3-hour IV infusion on Day 2 and Day 3; Switch to oral administration of fosmanogepix 800 mg QD on Day 4 to Day 7.	**Maintenance oral dose:** Placebo QD via 3-hour IV infusion on Day 2 and Day 3; Switch to oral administration of placebo QD on Day 4 to Day 7.

IV = intravenous; BID = twice daily; QD = once daily.

6.1.1 Administration

6.1.1.1 PART-1: Single dose

In PART-1, subjects will be enrolled in two cohorts and randomized to fosmanogepix (including a low dose and a high dose in each cohort) or placebo.

- Cohort 1: subjects will receive oral administration of 400 mg fosmanogepix, 800 mg fosmanogepix, or placebo on Day 1 (as shown in Table 5).
- Cohort 2: subjects will receive a 3-hour IV infusion of 600 mg fosmanogepix, 1,000 mg fosmanogepix, or placebo on Day 1 (as shown in Table 5).

6.1.1.2 PART-2: Multiple dose

In PART-2, subjects will be enrolled in two cohorts and randomized to fosmanogepix or placebo:

- All subjects (Cohort 3 and Cohort 4) will receive a 3-hour IV infusion (1,000 mg fosmanogepix or placebo, BID) 12 hours (±10 minutes) apart on Day 1.
- In Cohort 3, subjects will receive the maintenance dose of 600 mg fosmanogepix or placebo, 3-hour IV infusion QD from Day 2 to Day 7.
- In Cohort 4, subjects will receive the maintenance dose of 600 mg fosmanogepix or placebo, 3-hour IV infusion, QD on Day 2 and Day 3, and switch to oral administration of 800 mg fosmanogepix or placebo QD from Day 4 to Day 7.

6.1.1.3 Both PART-1 and PART-2

- For oral administration days, study drug must be administered in accordance with the Pharmacy Manual with ambient temperature water to a total volume of approximately 240 mL. Subjects are to swallow the study drug whole and will not manipulate or chew the study drug prior to swallowing. Clinical site personnel will examine each subject's mouth and hands to ensure that the study drug was ingested.
- For both Cohort 3 and Cohort 4, the first maintenance dose should be administered (start time) within 12 hours (±10 minutes) of the start of last dose on Day 1, and the next maintenance dose (start time) should be administered within 24 hours (±10 minutes). For all IV-infusions, the maximum infusion duration is 3 hours (±5 minutes).

6.2 Preparation, handling, storage, and accountability

1. The Investigator or designee must confirm that appropriate conditions (e.g., temperature) have been maintained during transit for all study drug received, and that any discrepancies are reported and resolved before use of the study drug.
2. Only subjects enrolled in the study may receive study drug and only authorized site staff may supply, prepare, or administer study drug.
3. All study drug must be stored in a secure, environmentally-controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff while respecting the procedure to maintain the blind. Daily minimum and maximum temperatures, including in nonworking days, for all site storage locations must be documented and must be available on request.
4. Any excursions from the study drug label storage conditions should be reported to the Sponsor upon discovery, along with actions taken. The site should actively pursue options for returning the study drug to the labeled storage conditions as soon as possible. Once an excursion is identified, the study drug must be quarantined and not used until the Sponsor provides permission to use the study drug. Specific details regarding the excursion definition and information to report for each excursion are provided to the site in the Pharmacy Manual.

5. Any storage conditions stated in the IB are superseded by the storage conditions stated on the label. See the Pharmacy Manual for storage conditions of the study drug once reconstituted and/or diluted.
6. Study drug should be stored in its original containers.
7. The Investigator or authorized site staff is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records), such as the Accountability Log as described in the Pharmacy Manual. All study drug must be accounted for using a study drug accountability form/record.
8. Further guidance and information for the final disposition of unused study drug is provided in the Pharmacy Manual. All destruction must be adequately documented. If destruction is authorized to take place at the clinical site, the Investigator or authorized site staff must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any instructions provided by the Sponsor.

If a product complaint is identified, the Sponsor must be notified within 1 business day of discovery in accordance with the Pharmacy Manual.

6.2.1 Preparation and dispensing

Fosmanogepix or placebo must be prepared by qualified unblinded site personnel in accordance with the Pharmacy manual. Intravenous and oral study drug should be prepared and masked (if applicable) and dispensed by an appropriately qualified and experienced unblinded member of the study staff in a manner which prevents accidental unblinding of the blinded study staff who will administer the study drug (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) in accordance with applicable guidance. A second unblinded staff member must verify the dispensing.

6.3 Assignment to study drug

All subjects signing the ICF will be assigned a subject number in the Electronic Data Capture (EDC). On Day 1 prior to the first study drug administration, eligible subjects will be randomized.

In PART-1, 32 subjects (16 in Cohort 1, then 16 in Cohort 2) will be randomized in a 3:3:2 ratio to FMGX low-dose, FMGX high-dose, or Placebo. In PART-2, 20 subjects (10 in Cohort 3 and 10 in Cohort 4) will be randomized in a 4:1 ratio to FMGX or Placebo.

Assignment to a specific treatment arm will be controlled by the Medidata Randomization and Trial Supply Management (RTSM) system, integrated with RAVE EDC.

6.4 Blinding of study drug

This study will be double-blind with regard to the administration of study drugs, i.e., will be blinded to the subjects, Sponsor staff / contract research organization staff, Investigator,

and other site staff. To ensure that the blinding is maintained, only the following personnel may have access to details of the treatment allocation:

- those setting up the randomization scheme and RTSM
- the unblinded pharmacist/designee responsible for blinded study drug preparation and documentation
- those required to break the blind for the purposes of expedited reporting to health authorities and other relevant institutions
- those responsible for unblinded monitoring of study drug preparation and accountability, and their supervisors
- those responsible for measuring plasma concentrations of fosmanogepix and manogepix

These personnel must not disclose any details of the randomization scheme or treatment allocation.

Blood samples will be obtained from all subjects for PK analysis to maintain the study blind, but samples from subjects randomized to placebo will not be routinely analyzed.

The unblinded pharmacist/designee will prepare IV and oral study drug in such a way that investigators, subjects, and staff directly involved in subject's management will remain blinded to the IV and oral study drug being administered. Infusion bags will be labeled with a study drug label provided by the Sponsor and in accordance with applicable regulatory requirements. The pharmacy will be monitored by an unblinded monitor.

It is important that the identity of both IV and oral study drug is not revealed to any other persons during the study except for those authorized as stated above.

In the event of a Quality Assurance audit, the auditors must be allowed access to unblinded study drug records at the site to verify that randomization/dispensing has been done accurately.

Details are described in the Pharmacy Manual.

6.4.1 Breaking the blind

The RTSM will be programmed with blind-breaking instructions. In the event of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a subject's treatment assignment, unless this could delay further management of the subject's safety. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind, and the date and reason that the blind was broken must be recorded in the source documentation and eCRF. Only a minimum number of necessary staff should have access to the unblinding information.

6.5 Study drug compliance

When subjects are dosed at the clinical site, they will receive study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinical site will be recorded in the source documents and recorded in the eCRF. The dose of study drug and study subject identification will be confirmed at the time of dosing by a member of the clinical site other than the person administering the study drug. For the oral administration, clinical site personnel must examine each subject's mouth and hands to ensure that the study drug was ingested.

A record of the number of study drug vials/tablets dispensed to and taken by each subject must be maintained and reconciled with study drug and compliance records according to the Pharmacy Manual.

6.6 Dose modification

No dose modification is planned in this study.

6.7 Continued access to study drug after the end of the study

No study drug will be provided to subjects after their participation in the study.

6.8 Treatment of overdose

Study drug greater than 5% than the protocol-defined dose on a daily basis will be considered an overdose.

There is no specific treatment for an overdose. In the event of an overdose, the Investigator or designee must:

1. Contact the Medical Monitor within 24 hours.
2. Closely monitor the subject for any AEs and laboratory abnormalities as medically appropriate for at least five half-lives or 28 calendar days (whichever is longer) after the overdose of study drug.
3. Document the quantity and duration of the excess dose in the eCRF.
4. Report the overdose as an SAE only if it otherwise meets the definition of an SAE in Appendix 3.
5. Obtain a blood sample for PK analysis within 7 days from the date of the last dose of study drug if requested by the Medical Monitor (determined on a case-by-case basis).

6.9 Prior and Concomitant medications

Use of prescription or non-prescription drugs and dietary and herbal supplements is prohibited from Screening, or within five half-lives prior to the first dose of study drug (whichever is longer), and throughout the study, except for hormonal contraceptives (see Appendix 4) and for the management of AEs (e.g., antiemetics for treatment and/or prevention of nausea or vomiting). This includes all vaccines, vitamins, herbal supplements, or remedies. Limited use of non-prescription medications that are not considered to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the Sponsor.

Hormonal contraceptives that meet the requirements of this study are allowed to be used by women of childbearing potential (see Appendix 4).

All medications taken within 28 days before the first dose of study drug and during the study must be recorded in the source documents and in the eCRF, including indication, dose, frequency of administration, route of administration, and start and stop dates of administration. All subjects are to be asked about concomitant medications at each clinic visit.

7 DISCONTINUATION OF STUDY DRUG AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study drug

It may be necessary for a subject to permanently discontinue receipt of study drug. Reasons for permanent discontinuation of receipt of study drug include the following:

- AE requiring discontinuation in the Investigator's view
- Pregnancy
- Requirement for prohibited concomitant medications
- The subject requests discontinuation from the study for any reason or withdraws consent

Note that discontinuation of study drug does not in itself represent withdrawal from the study (see Section 7.2). If study drug is permanently discontinued, the subject may remain in the study to be evaluated for safety. See the Schedule of assessments for data to be collected at the time of discontinuation of study drug and follow-up for any further evaluations that need to be completed.

Discontinuation of study drug must be documented in the eCRF and in the source documents whether the subject is only discontinuing further receipt of study drug, or is also discontinuing from study procedures, post-treatment follow-up, and/or future collection of additional information.

7.1.1 ECG changes

A subject who meets either of the following criteria based on the average of triplicate ECG readings must be discontinued from the study drug.

- QTcF $\geq$ 500 msec or
- Change from baseline: QTcF $\geq$ 60 msec and QTcF > 450 msec.

If a clinically significant ECG finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the Investigator or designee must determine whether the subject may continue in the study, and whether any change in management is needed. In such cases the review of the ECG printed at the time of collection must be documented, and any new clinically relevant finding must be reported as an AE.

7.2 Subject discontinuation/withdrawal from the study

A subject is considered to have completed the study if he/she has completed all periods of the study, including the last scheduled procedure shown in the Schedule of assessments.

A subject may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include:

- Subject refuses further study procedures
- Subject is lost to follow-up
- Death
- The study is terminated by the Sponsor
- Investigator's decision to withdraw the subject from the study

At the time of discontinuation from the study, an early discontinuation visit should be conducted if possible. See the Schedule of assessments for assessments to be collected at the time of study discontinuation and follow-up, and for any further evaluations that need to be completed.

If a subject withdraws from the study, he or she may request destruction of any remaining samples taken and not tested. The Investigator must document any such requests in the site study source documents, and notify the Sponsor accordingly.

If the subject withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations may be performed, and no additional data may be collected. The Sponsor may retain and continue to use for the purposes of the study, any data collected before consent was withdrawn.

7.2.1 Withdrawal of consent

If a subject specifically withdraws consent for any further contact with him or her, this should, if possible, be obtained in writing. The withdrawal of consent should be documented in detail in the source documents by the Investigator or designee, and entered on the appropriate eCRF page.

7.3 Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical site.

The following actions must be taken if a subject fails to attend a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible. The subject should be counseled on the importance of maintaining the assigned visit schedule, and whether the subject wishes to and/or should continue in the study should be ascertained.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (comprising, where possible, at least

three telephone calls and, if necessary, a certified letter to the subject's last known mailing address, or local equivalent methods). These contact attempts should be documented in the subject's source documents.

- If the subject continues to be unreachable, he or she will be considered to be lost to follow-up and discontinued from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

The Investigator or designee must obtain a signed and dated ICF before performing any study-specific procedures.

Study procedures and their timing are summarized in the Schedule of assessments. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the Sponsor immediately to determine whether the subject should continue or discontinue study drug.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator must maintain a screening log to record details of all subjects screened, and to confirm eligibility or record reasons for screening failure, as applicable.

Subjects will be screened within 28 days prior to administration of the first study drug to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (e.g., delayed drug shipment), then subjects do not require rescreening if the laboratory results obtained prior to first dose administration meet the eligibility criteria.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator must take all steps necessary to ensure the safety and wellbeing of the subject. When a protocol-required test cannot be performed, the Investigator must document the reason for the missed test and any corrective and preventive actions taken to ensure that required processes are adhered to as soon as possible. The Sponsor study team must be informed of these incidents in a timely manner.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments should be collected prior to the insertion of the catheter.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the clinical site prior to initiation of the study.

The blood sampling volume of an individual subject for PK assessment in PART-1 is approximately 84 mL (including PPB samples), and in PART-2 is approximately 88 mL. Other blood sampling volume for safety or other assessments depend on the clinical site clinical practice requirements. Additional blood samples may be taken for safety

assessments at times specified by the Sponsor or Investigator, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

To prepare for study participation, subjects must be instructed on the information on lifestyle considerations in Section 5.3, and on the prior and concomitant medications in Section 6.9.

8.1 Efficacy assessments

There are no efficacy assessments as the efficacy of fosmanogepix is not under investigation in this study.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of assessments. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1 Physical examinations

A complete physical examination must include head, ears, eyes, nose, mouth, skin, heart, and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination must include assessments of general appearance, the respiratory, cardiovascular, and neurology systems, and subject-reported symptoms.

These physical examinations must be conducted by a physician.

Physical examination findings collected during the study will be considered source data and will not be required to be reported in the eCRF, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

Height and weight will be measured and recorded at Screening only to calculate body mass index (BMI). For measuring weight, a scale with appropriate range and resolution is to be used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight. Height and weight including date and time of the measurements are to be recorded in both source documents and eCRF.

8.2.2 Vital signs

Vital signs include BP, PR, temperature, respiratory rate, and oxygen saturation.

Supine BP should be measured with the subject's (preferably dominant) arm supported at the level of the heart, and recorded to the nearest mmHg after at least 5 minutes of rest. If possible, the same arm should be used throughout the study. Blood pressure should not be taken from the arm with an intravenous infusion. Subjects should be instructed not to

speak during measurements. If an IV catheter is utilized for blood sampling collections, vital sign assessments (BP and PR) should be collected prior to insertion of the catheter.

The same properly sized and calibrated BP cuff is to be used to measure BP each time. While the use of an automated device for measuring BP and PR is acceptable, when done manually, PR is to be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the blood collection.

Additional collection times, or changes to collection times, of BP and PR are permitted as necessary to ensure appropriate collection of safety data.

Temperature will be measured by the method according to the Investigator's discretion, provided the same method is used and documented throughout the study. No eating or drinking is allowed for 15 minutes prior to the measurement.

Respiratory rate and oxygen saturation will be measured by the method according to the Investigator's discretion, provided the same method is used and documented throughout the study.

Vital signs data (i.e., BP, PR, temperature, respiratory rate, and oxygen saturation) including date and time of the measurements are to be recorded in both source documents and eCRF.

8.2.3 Electrocardiograms

ECG values of potential clinical concern are listed in Appendix 6.

Standard 12-lead ECGs utilizing limb leads with a 10-second rhythm strip should be performed at times specified in the Schedule of assessments, using an ECG machine that automatically calculates HR and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (e.g., Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the subject has rested quietly for at least 5 minutes in a supine position. If an IV catheter is utilized for blood sampling collections, ECGs should be collected prior to insertion of the catheter.

To ensure the safety of the subjects, a qualified individual at the clinical site must compare ECG results with baseline measurements. Additional ECG monitoring is to be performed if a) a post-dose QTcF interval is increased by $\geq$ 60 msec from the baseline and is $>$ 450 msec; or b) an absolute QT value is $\geq$ 500 msec for any scheduled ECG. If either of these conditions is met, two additional ECGs are to be performed approximately 2 to 4 minutes apart to confirm the original measurement. If the QT/QTcF values from these repeated ECGs remain above the threshold values, then a single ECG must be repeated at least hourly for a maximum of 4 hours until QT/QTcF values from two successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains $\geq$ 60 msec from the baseline and is $>$ 450 msec; or b) an absolute QT value is $\geq$ 500 msec for any scheduled ECG for more than 4 hours

(or sooner, at the discretion of the Investigator); or c) QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to below these criteria after 8 hours of monitoring (or sooner, at the discretion of the Investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECGs must be assessed by the investigator/designee for any abnormalities, including prolongation of QTcF. The ECG printouts are to be signed and dated by the Investigator. ECG data, including date and time of the measurements, are to be recorded in the eCRF.

8.2.4 Clinical safety laboratory assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed, and the Schedule of assessments for the timing and frequency. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless these are judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 – 35 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.

If such values do not return to normal or baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

The clinical safety laboratory data, including date and time of assessment, are to be recorded in the eCRF.

8.2.5 Pregnancy testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests are to be performed for women of childbearing potential at the times listed in the Schedule of assessments. Following a negative pregnancy test result at Screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at Day –1 prior the subject receiving the first study

drug. Pregnancy tests must also be done whenever one menstrual cycle is missed during the active collection period (or when potential pregnancy is otherwise suspected), and at the end of the study. If a urine test cannot be confirmed as negative (e.g., the result is ambiguous), a serum pregnancy test is required.

8.3 Adverse events, serious adverse events, and other safety reporting

The definitions of an AE and an SAE are provided in Appendix 3.

During the active collection period as described in Section 8.3.1, each subject will be questioned about the occurrence of AEs in a non-leading manner.

Adverse events may arise from symptoms or other complaints reported to the Investigator by or on behalf of the subject, or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc.).

The Investigator is responsible for the detection, documentation, and recording of events that meet the definition of an AE, and for obtaining adequate information, including follow-up information where applicable, to determine the outcome and to assess whether the event meets the criteria for classification as an SAE, or is the reason for discontinuation of the study drug (see Section 7.1).

8.3.1 Time period and frequency for collecting AE and SAE information

The time period for actively collecting AEs and SAEs (the 'active collection period') for each subject begins from the time the subject provides informed consent, through and including 28 – 35 days after the last administration of the study drug.

If there is an unresolved AE at the end of the active collection period, follow-up by the Investigator continues until the AE or its sequelae resolve or stabilize at a level acceptable to the Investigator. After follow-up visit, information on AEs will only be recorded on source documents (except in case of SAE as described in Section 8.3.1.1).

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

If the subject withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a subject temporarily or permanently discontinues study drug because of an AE, the AE must be recorded in the eCRF, and if an SAE, must also be reported using the SAE Report Form.

The Investigator is not required to actively seek information on AEs after the subject has concluded study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has completed the study, and considers the event to be reasonably related to the study drug, the Investigator must promptly report the SAE to the Sponsor using the SAE Report Form.

8.3.1.1 Reporting SAEs to the Sponsor

All SAEs occurring during the active collection period must be reported to the Sponsor on the SAE Report Form immediately upon awareness, and under no circumstances more than 24 hours later, as indicated in Appendix 3. The Investigator must submit any updated SAE data to the Sponsor within 24 hours of it being available.

8.3.1.2 Recording AEs and SAEs in the eCRF

All AEs and SAEs occurring during the active collection period must be recorded in the AE section of the eCRF.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE or SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. For each event, the Investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (see Section 7.3).

Follow-up information must include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted to the Sponsor as soon as possible.

Information related to SAEs must also be reported to the Sponsor within 24 hours of their knowledge of their event.

Further information on follow-up procedures is given in Appendix 3.

8.3.4 Regulatory reporting requirements for SAEs

Notification of an SAE within 24 hours by the Investigator to the Sponsor is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study drug under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor must comply with applicable legislative and regulatory requirements relating to the safety reporting to Health Authorities, Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs), and Investigators.

The Sponsor is responsible for preparing Investigator safety reports for suspected unexpected serious adverse reactions (SUSARs) in accordance with local regulatory requirements, and for forwarding them to Investigators as necessary.

An Investigator who receives SUSARs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor must review the information and then file it with the RSIs for the study, and must notify the IRB/IEC, as applicable in accordance with local requirements.

8.3.5 Environmental exposure, exposure during pregnancy or breastfeeding, and occupational exposure

Environmental exposure occurs when a person not enrolled in the study as a subject receives unplanned direct contact with, or exposure to, the study drug. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study drug is reportable to the Sponsor via SAE Report Form within 24 hours of the Investigator becoming aware of it, regardless of whether there is an associated SAE. Since the exposure information does not pertain to the subject enrolled in the study, the information is not recorded in the eCRF; however, a copy of the completed SAE Report Form is maintained in the Investigator Site File.

8.3.5.1 Exposure during pregnancy

An exposure during pregnancy occurs if:

- A female subject is found to be pregnant while receiving, or up to 28 days after discontinuing, study drug.
- A female who is not enrolled in the study is found to be pregnant while being exposed to, or having been exposed to, study drug due to environmental exposure. For example, if a female family member or healthcare provider reports that she is pregnant after having been exposed to the study drug by ingestion or up to 28 days after exposure.

If exposure during pregnancy occurs in a subject, the Investigator must report this information to the Sponsor on the SAE Report Form and on the Pregnancy Report Form, regardless of whether an SAE has occurred. Details of the pregnancy must be collected after the start of study drug and until 28 – 35 days after the last dose.

If exposure during pregnancy occurs in the setting of environmental exposure, the Investigator must report the information to the Sponsor using the SAE Report Form and Pregnancy Report Form. Since the exposure information does not pertain to a subject enrolled in the study, the information is not recorded in the eCRF; however, a copy of the completed SAE Report Form is to be maintained in the Investigator Site File.

The Investigator must report exposure during pregnancy to the Sponsor within 24 hours of the Investigator's awareness, regardless of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is to be conducted to obtain general information on the pregnancy and its outcome. The Investigator must follow the pregnancy until completion or termination, and must notify the Sponsor of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate should be assessed at the time of birth and at 8 weeks after delivery. In the event of a termination, if known, the reasons for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the Investigator must follow the procedures for reporting SAEs. Important to consider in regard to these SAEs:

- Spontaneous abortion including includes miscarriage and missed abortion.
- A death that occurs within 8 weeks after birth must be reported as an SAE, regardless of causality.
- A death that occurs later than 8 weeks after birth must be reported as an SAE when the Investigator assesses the death as related or possibly related to exposure to the study drug.

Additional information regarding the exposure during pregnancy may be requested by the Sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

8.3.5.2 Exposure during breastfeeding

Patients who are breastfeeding are excluded from this study. If a female patient is found to be breastfeeding while receiving or 14 days after discontinuing study drug this has to be reported to the Sponsor within 24 hours of the investigator's awareness using the SAE paper Report Form, irrespective of whether an SAE has occurred.

8.3.5.3 Occupational exposure

The Investigator must report any instance of occupational exposure to the Sponsor within 24 hours of the Investigator's awareness, using the SAE Report Form, regardless of whether there is an associated SAE. As the information about the occupational exposure does not pertain to a subject enrolled in the study, the information is not recorded on a eCRF; however, a copy of the completed SAE Report Form is to be maintained in the Investigator Site File.

8.3.6 Adverse events of special interest

Adverse events of special interest (AESIs) for the purposes of this study include CNS toxicity, liver toxicity, testicular toxicity, and embryofetal toxicity. In this study, AESIs will be identified by the Sponsor using Standardized MedDRA Queries (SMQs) and/or selection of Preferred Term.

These AESIs are to be examined as part of routine safety data review procedures throughout the clinical study, and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.3. An AESI is to be recorded as an AE or SAE in the eCRF, and an AESI that is also an SAE must be reported using the SAE Report Form.

8.3.7 Medication errors (including overdose)

Medication error is an unintended failure in the drug administration process that leads to, or has the potential to lead to, harm to the patient. All AEs associated with the medication error should be recorded on the eCRF AE page. Medication errors which are associated with an SAE must also be reported on an SAE Report Form to the Sponsor within 24 hours of awareness of the event.

Medication errors include, but are not limited to:

- Wrong patient exposure to the study drug
- Unintentional error in applying the dosage regimen foreseen in the protocol
- Unintentional administration of expired study drug
- The administration of an incorrect study drug
- Unintentional administration of study drug that has undergone temperature excursion from the specified storage range, unless it is determined by the Sponsor that the study drug under question is acceptable for use.

8.4 Pharmacokinetics

8.4.1 Plasma for analysis of fosmanogepix and manogepix

If an indwelling catheter is used, approximately 3× the device dead volume of blood is to be discarded prior to PK blood collection at each sample collection time point. This blood volume would be in addition to the volumes reported above.

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL plasma, will be collected for measurement of plasma concentrations of fosmanogepix (prodrug) and manogepix (active moiety). Instructions for the collection and handling of biological samples are provided in the Laboratory Manual or by the Sponsor. The actual date and time (using 24-hour clock time) of each sample must be recorded.

While the actual times of sampling may vary, the number of samples must remain as specified in the PK Sampling Schedules in the Schedule of assessments. All efforts must be made to obtain the samples at the exact nominal time relative to dosing.

- Collection of samples up to and including 4 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (e.g., within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted in the source document and the eCRF.
- Collection of samples more than 4 hours and up to and including 10 hours after dose administration that are obtained ≤ 30 minutes away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and in the eCRF.
- Collection of samples more than 10 hours and up to and including 100 hours after dose administration that are obtained ≤ 1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and in the eCRF.
- Collection of samples more than 100 hours after dose administration that are obtained ≤ 3 hours away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and in the eCRF.

Samples will be used to evaluate the PK of fosmanogepix and manogepix; samples collected for analyses of fosmanogepix and manogepix plasma concentration may also be used to evaluate safety concerns arising during or after the study, for metabolite identification, and/or for evaluation of the bioanalytical method.

Samples collected for measurement of plasma concentrations of fosmanogepix and manogepix will be analyzed using validated analytical methods in compliance with applicable SOPs.

All PK samples must be processed and shipped as indicated in the instructions provided to the clinical site, to maintain sample integrity. Any deviations from the PK sample handling procedure, including sample collection and processing steps, interim storage conditions, and shipping conditions, and any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised.

8.4.2 Plasma for determination of manogepix unbound fraction

If an indwelling catheter is used, approximately 3× the device dead volume of blood is to be discarded prior to blood collection for PPB at each sample collection time point. This blood volume would be in addition to the volumes reported above.

Blood samples of approximately 12 mL, to provide sufficient plasma (approximately 5 mL) for unbound fraction determination, will be collected. Instructions for the collection and handling of biological samples are provided in the Laboratory Manual or by the Sponsor. The actual date and time (using 24-hour clock time) of each sample must be recorded.

While the actual times of sampling may vary, the number of samples must remain as specified in the PK Sampling Schedules in the Schedule of assessments. All efforts must be made to obtain the samples at the exact nominal time relative to dosing.

- Collection of samples up to and including 4 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (e.g., within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and in the eCRF.

The samples for determination of manogepix plasma protein binding must be processed and shipped as indicated in the instructions provided to the clinical site, to maintain sample integrity. Any deviations from the sample handling procedure, including sample collection and processing steps, interim storage conditions, and shipping conditions, and any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised.

8.5 Genetics

No specified genetic analyses are planned for this study.

8.6 Biomarkers

No specified biomarker analyses are planned for this study.

9 STATISTICAL CONSIDERATIONS

The detailed methodology for summary and statistical analyses of the data collected in this study is outlined here, and further detailed in the Statistical Analysis Plan (SAP), which will be maintained by the Sponsor. The SAP may modify what is outlined in the protocol where appropriate; any major modifications of the primary endpoint definitions or their analyses must also be reflected in a protocol amendment.

9.1 Statistical hypotheses

No statistical hypotheses will be tested in this study.

9.2 Analysis sets

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

PK analysis set

The PK analysis set comprises all randomized subjects who receive at least one dose of study drug and who have at least one post-baseline measurable concentration of manogepix.

Safety analysis set

The Safety analysis set comprises all randomized subjects who receive at least one dose of study drug. Subjects will be analyzed according to the drug they actually received.

9.3 Statistical analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1 Pharmacokinetic analysis

Pharmacokinetic analyses will be performed using the PK analysis set.

9.3.1.1 Derivation of pharmacokinetic parameters

The plasma PK parameters for manogepix and fosmanogepix will be derived from the concentration-time profiles as detailed in Table 6 and Table 7, using actual PK sampling times. In the event that actual PK sampling times are not available, nominal PK sampling times will be used instead.

Table 6 Plasma PK parameters for PART-1: Single-dose

Parameter	Analyte	Definition	Method of determination
AUC_{0-24h}	Manogepix/ fosmanogepix*	Area under the plasma concentration-time profile from time zero to 24 hours	Linear/log trapezoidal method.
AUC_{last}	Manogepix/ fosmanogepix*	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C_{last})	Linear/log trapezoidal method.
AUC_{inf}*	Manogepix	Area under the concentration-time curve from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}^*/k_{el})$, where C_{last}^* is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis.
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
$t_{½}$*	Manogepix	Terminal elimination half-life	$Log_e(2)/k_{el}$, 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	$Dose/AUC_{inf}$.
CL/F* (Cohort 1 only)	Manogepix	Apparent clearance	$Dose/AUC_{inf}$.
V_{ss}* (Cohort 2 only)	Manogepix	Volume of distribution at steady state	CL × 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	$Dose/(AUC_{inf} \times k_{el})$.
F*	Manogepix	Absolute bioavailability	$AUC_{inf,po}$(dose normalized) (mean value in Cohort 1) / $AUC_{inf,iv}$(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 7 Plasma PK parameters for PART-2: Multiple-dose

Parameter	Analyte	Definition	Method of determination
AUC_{tau}	Manogepix	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.
AUC_{0-24h}	Fosmanogepix*	Area under the plasma concentration-time profile from time zero to 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.
$t_{½}$*	Manogepix	Terminal elimination half-life	$Log_e(2)/k_{el}$, 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	Dose/AUC_{tau}.
CL/F* (Cohort 4 only)	Manogepix	Apparent clearance	Dose/AUC_{tau}.
V_{ss}* (Cohort 3 only)	Manogepix	Volume of distribution at steady state	CL × 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	Dose/(AUC_{tau}×k_{el}).
C_{trough}	Manogepix	Pre-dose concentration	Observed directly from data obtained on Day 7 and Day 8 (24 hours after last dose) #.
F	Manogepix	Absolute bioavailability	$AUC_{tau,po}$(dose normalized) (mean AUC_{tau} in Cohort 4) / $AUC_{tau,iv}$(dose normalized) (mean AUC_{tau} in Cohort 3)

* As data permit.
\# Other pre-dose concentrations will be collected on Day 1 (second dose), Day 2, Day 3, and Day 6.

9.3.1.2 Statistical methods for pharmacokinetic data

The data from PART-1 and PART 2 of the study will be analyzed and reported separately. The statistical summaries and plots will be presented by analyte (manogepix and fosmanogepix), cohort, and in PART-1 by dose level.

Plasma concentrations of manogepix and fosmanogepix (if available) will be summarized by nominal PK sampling times. Summary statistics in the tabulation will include n, mean, standard deviation, CV%, median, minimum, and maximum. Individual subject and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted using actual and nominal sampling times, respectively.

Plasma PK parameters (if available) will be described in a separate PK analysis plan. For AUCs and C_{max}, box and whisker plots for individual subject parameters overlaid with geometric means will be plotted. In PART-2, trough concentrations over time will be plotted for manogepix by study day.

Fraction of unbound drug in plasma (f_u) will be listed and summarized descriptively by cohort and dose level.

9.3.2 Safety analyses

All safety analyses will be performed using the Safety analysis set. The data from PART-1 and PART 2 of the study will be analyzed and reported separately. The safety analyses will be presented in tabular and/or graphical format, and summarized descriptively by cohort and treatment group. Data from subjects on placebo will be pooled together for PART-2 (Cohort 3 and Cohort 4) analysis.

Adverse events, ECGs, vital signs, and safety laboratory data will be reviewed during the study to evaluate the safety of subjects.

Physical examination information collected during the study, will be considered source data and will not be reported, except any untoward findings during the active collection period which meet the definition of an AE. Data collected at Screening that are used for inclusion/exclusion criteria, such as medical history, laboratory data, ECGs, and vital signs, as well as demographic data will be reported as stated above.

9.3.2.1 Electrocardiogram analyses

Changes from baseline for the ECG parameters QT interval, HR, QTcF interval, PR interval, and QRS complex will be summarized by timepoint.

The number (%) of subjects with maximum post-dose QTcF values and maximum increases from baseline in the following categories will be tabulated.

Table 8 Safety QTcF assessment

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

9.4 Interim analyses

No formal interim analysis will be conducted for this study.

9.5 Sample size determination

9.5.1 PART-1: Single-dose

A sample size of approximately sixteen 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.

9.5.2 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.

10 PROTOCOL VERSION HISTORY

Date	Version	Summary of changes
11 February 2022	1.0	Original protocol (Sponsor: Pfizer)
30 October 2024	2.0	Fully revised protocol (Sponsor: Basilea)
18 March 2025	3.0	See Protocol Amendment 1

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12 APPENDICES

Appendix 1 Regulatory, ethical, and study oversight considerations

1. Regulatory and ethical considerations

This study must be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations, including applicable data protection / privacy laws

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be reviewed and approved by the Sponsor, submitted to an IRB/IEC by the Investigator, and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to address an immediate hazard to study subjects.

Protocols and any substantial amendments to the protocol must have Health Authority approval prior to initiation except for changes necessary to address an immediate hazard to subjects.

The Investigator is responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of the IRB/IEC, applicable laws and regulations, and ICH GCP Guidelines.

Reporting of safety issues and serious breaches

In the event of any prohibition or restriction imposed on the study by an applicable Health Authority in any jurisdiction (e.g., a clinical hold), or if the Investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study drug, the Sponsor must be informed immediately.

In addition, the Investigator must inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP guidelines that the Investigator becomes aware of.

2. Financial disclosure

The Investigator and sub-investigators must provide the Sponsor with sufficient, accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authority. The Investigator is responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

3. Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the potential subjects, and answer all questions regarding the study. The subject should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the study.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The Investigator must ensure that each subject is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the subject's personal data.

The subject must be informed that their personal study-related data will be used by the Sponsor in accordance with applicable data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from Health Authorities.

The Investigator must also ensure that each subject is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study, and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be reconsented (asked to re-sign) the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject. A potential subject in the study who is rescreened after signing an ICF is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

4. Data protection

All parties must comply with all applicable laws, including laws regarding the protection of privacy / personal subject data.

Subjects' personal data will be stored at the clinical site in encrypted electronic and/or paper form, and must be password-protected or secured in a locked room to ensure that only authorized study staff have access. The site must implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the clinical site will be responsible for determining whether a personal data breach has in fact occurred and, if so, for providing breach notifications as required by law.

To protect the rights and freedoms of subjects with regard to the processing of personal data, subjects will be assigned a single, subject-specific numerical code. Any subject records or datasets that are transferred to the Sponsor must contain the numerical code; subject names must not be transferred. All other identifiable data transferred to the Sponsor will be identified by this single, subject-specific code. The clinical site must maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity and medical record ID. In case of data transfer, the Sponsor must protect the confidentiality of subjects' personal data consistent with the clinical study agreement and applicable privacy laws.

5. Committees structure

Data Monitoring Committee

This study will not use a Data Monitoring Committee.

6. Dissemination of clinical study data

The Sponsor may publicly disclose clinical study information and results through posting on ClinicalTrials.gov, the EU Clinical Trials Information System (CTIS), and other public registries and websites in accordance with applicable laws and regulations.

7. Data quality assurance

All subject data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

Guidance on completion of eCRFs will be provided in the eCRF Completion Guidelines.

The Investigator must ensure that the eCRFs are securely stored at the clinical site in encrypted electronic and are password-protected to prevent access by unauthorized third parties.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and Health Authority inspections, and must provide direct access to source data documents. This verification may also occur after study completion. It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and

possible audits or inspections, and that sufficient time is devoted to the process. The investigator and relevant personnel must promptly address, in collaboration with the Sponsor, any issue, gap, finding, or deviation identified during study-related monitoring and/or audits.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the Monitoring Plan and Quality Risk Management Plan maintained and utilized by the Sponsor.

The Sponsor is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICFs, pertaining to the conduct of this study, must be retained by the Investigator for 25 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor. The Investigator must ensure that the records continue to be stored securely for as long as they are maintained.

The Investigator must notify the Sponsor immediately of any regulatory inspection notification in relation to the study. The Investigator must cooperate with the Sponsor to prepare the clinical site for the inspection, and must allow the Sponsor, whenever feasible, to be present during the inspection. The Investigator must promptly resolve any discrepancies identified between the study data and the subject's medical records, and must promptly provide copies of the inspection findings to the Sponsor. Before response submission to a Health Authority, the Investigator must provide the Sponsor with an opportunity to review and comment on responses to any such findings.

8. Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the clinical site.

Data entered in the eCRF that are from source documents must be consistent with the source documents, or any discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must be available.

Definition of what constitutes source data and its origin can be found in the study Source Data Location document, which is maintained by the clinical site.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of subjects are being protected, and that the study is being conducted in accordance with the protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

9. Study and site start and closure

The beginning of the study is defined when the first subject signs the ICF.

The end of the study is defined in Section 4.4 as the date of last visit of the last subject in the study.

The Sponsor reserves the right to close the clinical site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Sites will be closed upon study completion. A clinical site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The Investigator may initiate clinical site closure at any time upon notification to the Sponsor or designee/CRO if requested to do so by the responsible IRB/IEC or if such termination is required to protect the health of study subjects.

Reasons for the early closure of a clinical site by the Sponsor may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or a Health Authority, the Sponsor's procedures, the ICH GCP guidelines, or applicable laws or regulations.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study drug development by the Sponsor.

If the study is prematurely terminated or suspended, the Sponsor must promptly inform the Investigators, the IRBs/IECs, the Health Authority, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator must promptly inform the subject, and should assure appropriate subject therapy and/or follow-up.

The definition of study termination is also provided in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will prevail as to termination rights.

10. Publication policy

The Sponsor will submit a summary of the results of the clinical study together with a summary that is understandable to a layperson, and the clinical study report, where applicable, within the defined timelines.

The results of this study will be made available, e.g., submitted for publication and/or presentation at scientific meetings, in a timely manner. All manuscripts or abstracts must be submitted to the Sponsor prior to publication or presentation, allowing the Sponsor to

protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10. Sponsor's responsible Medical Monitor

The contact information for the Sponsor's responsible Medical Monitor for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to their Investigator and the Sponsor's responsible Medical Monitor for study related medical questions or problems from non-study healthcare professionals, subjects are provided with an Emergency Contact Card (ECC) at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study drug blinded identifiers, (b) subject's study identification number, (c) site emergency phone number active 24 hours a day, 7 days a week.

The ECC is intended to augment, not replace, the established communication pathways between the subject and their Investigator and site staff, and between the Investigator and Sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the Investigator or site staff related to the care of a subject.

Appendix 2 Clinical safety laboratory tests

The following safety laboratory tests will be performed at times defined in the Schedule of assessments. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 9 Protocol-required safety laboratory assessments

Hematology	Clinical Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/Urea and creatinine Glucose Calcium Sodium Potassium Chloride CO_2CP or (CO_2) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	Local Dipstick: pH Glucose Protein Blood Ketones Nitrites Leukocyte esterase Laboratory: Microscopy[a]	• Urine drug screening[b] • Breath or urine alcohol test • Pregnancy test (hCG)[c] At Screening only: • FSH[d] • HBsAg • HBcAb • HCVAb • HIV • TPPA For suspected DILI: • AST/ALT • Tbili, direct and indirect bili • Total bile acids, GGT • Total protein, albumin • CK • PT, INR • Acetaminophen/paracetamol or protein adduct levels • Hepatitis serology (even if screening negative)

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site-specific).
c. Local urine pregnancy testing (hCG) will be standard for the protocol unless serum testing is required by local regulation or the IRB/IEC. Only conducted in female subjects of childbearing potential at times defined in the Schedule of assessments.
d. For confirmation of postmenopausal status only.

The Investigator must review the laboratory report, document this review, and record any clinically-relevant changes occurring during the study in the AE section of the eCRF.

Appendix 3 Adverse event definitions and procedures

1 DEFINITIONS

1.1 Definition of an adverse event

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

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated).

1.1.1 Events meeting the adverse event definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator. Any abnormal laboratory test results that meet any of the conditions below must be considered 'clinically significant' (Section 8.2.4) and recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical drug.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study drug administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication.

1.1.2 Events not meeting the adverse event definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless assessed by the Investigator as being more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): However, the condition that leads to the procedure is an AE.
- Situations in which no untoward medical occurrence occurred (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen.

1.2 Definition of a serious adverse event

A serious adverse event is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

(a) Results in death

(b) Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

(c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

(d) Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

(e) Is a congenital anomaly/birth defect

(g) Is medically significant

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

2 ADVERSE EVENT RECORDING AND REPORTING

2.1 Adverse event and serious adverse event recording and reporting

Table 10 summarizes the requirements for recording AEs in the eCRF and for reporting SAEs on the SAE Report Form to the Sponsor throughout the active collection period. These requirements are delineated for three types of events: (1) SAEs, (2) non-serious AEs, (3) exposure to the study drug during pregnancy or breastfeeding, and occupational exposure.

Table 10 AE and SAE recording and reporting

Safety Event	Recorded in the eCRF	Reported on the SAE Report Form to the Sponsor within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the study drug during pregnancy or breastfeeding	All AEs or SAEs associated with exposure during pregnancy or breastfeeding. Note: Instances of exposure during pregnancy or exposure during breastfeeding not associated with an AE or SAE are not captured in the eCRF.	All SAEs associated with exposure during pregnancy or breastfeeding should be reported on the SAE Report Form. All instances of exposure during pregnancy (whether or not there is an associated AE/SAE) must be reported on SAE Report Form and Pregnancy Form. All instances of exposure during breastfeeding (whether or not there is an associated SAE) must be reported on SAE Report Form.
Environmental (occupational/ accidental) exposure to the product under study to a non-subject.	None. Exposure to a non-study-subject is not collected in the eCRF.	The exposure (whether or not there is an associated AE or SAE) must be reported on SAE Report Form.

When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

The Investigator must then record all relevant AE or SAE information in the eCRF.

It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the SAE Report Form or AE or SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, must be redacted on the copies of the medical records before submission to the Sponsor.

The Investigator must attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

2.2 Assessment of severity

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE; these do not include the severity of the event.

Assessment of severity

The severity of all adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. These criteria can be found at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

For those adverse events not listed in the CTCAE, the following grading system should be used:

Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities.

Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable.

Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject's daily activities, or unacceptable.

Life-threatening (CTCAE Grade 4): Life threatening or disabling adverse event.

Death (CTCAE Grade 5): Death-related adverse event.

2.3 Assessment of causality

The Investigator must assess the relationship between study drug and each occurrence of each AE or SAE, using clinical judgment to determine the relationship.

A 'reasonable possibility' of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.

The Investigator should also consult the Investigator's Brochure and/or product information, for marketed products, in his/her assessment.

For each AE or SAE, the Investigator must document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

The Investigator may change his or her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

If the Investigator does not know whether or not the study drug caused the event, then the event will be handled as 'related to study drug' for reporting purposes, as defined by the Sponsor. In addition, if the Investigator determines that an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and eCRF, and report such an assessment in the dedicated section of the SAE Report Form and in accordance with the SAE reporting requirements.

2.4 Follow-up of adverse events and serious adverse events

The Investigator must perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the Sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

If a subject dies during participation in the study or during the follow-up period, the Investigator must provide the Sponsor with a copy of any postmortem findings, including histopathology.

New or updated information will be recorded in the originally submitted documents.

The Investigator must submit relevant updates to SAE data to the Sponsor within 24 hours of receipt of the information.

3 REPORTING OF SERIOUS ADVERSE EVENTS

All SAE Report Forms completed by the Investigator are to be sent to PrimeVigilance without undue delay but not later than within 24 hours of obtaining knowledge of the events. Email transmission of the SAE Report Form is the preferred method to transmit this information to PrimeVigilance. The contact details of PrimeVigilance are presented below:

PrimeVigilance contact details

Email: Basilea@primevigilance.com
EU eFax: + 44 8000 669 192
eFax: US toll free eFax: +1 866 902 7489
Copy: drug.safety@basilea.com

PrimeVigilance will confirm receipt within 1 business day. If this confirmation is not received please re send the SAE report form.

In circumstances when the email is not working, notification by facsimile or telephone is acceptable with a copy of the SAE Report Form sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE Report Form pages within the designated reporting time frames.

Appendix 4 Contraception

1. Male subject reproductive inclusion criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥ 100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

2. Female subject reproductive inclusion criteria

A female subject is eligible to participate in the study if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- The subject is not a woman of childbearing potential (WOCBP) (see definition below).

  OR

- The subject is a WOCBP and is using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described below from Screening until Follow-up visit, and for at least 28 days after the last dose of study drug, which corresponds to the time needed to eliminate any reproductive safety risk of the study drug. The Investigator should evaluate the effectiveness of the contraceptive method at Screening prior to the first dose of study drug.

  OR

- The subject is a WOCBP and is using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below from Screening until Follow-up visit, and for at least 28 days after the last dose of study drug, which corresponds to the time needed to eliminate any reproductive safety risk of the study drug. In addition, a second effective method of contraception must be used. The Investigator must evaluate the effectiveness of the contraceptive method at Screening prior to the first dose of study drug.

The Investigator is responsible for reviewing the subject's medical history, menstrual history, and recent sexual activity to decrease the risk of the inclusion in the study of a woman with an early undetected pregnancy.

3. Woman of childbearing potential

A woman is considered to be a WOCBP following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study drug, additional evaluation should be considered.

4. Women not considered to be of childbearing potential

A woman in any of the following categories is not considered to be a WOCBP:

- Premenopausal with one of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

  Note: Documentation for any of the above categories can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the subject's medical record for the study.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - In addition:
    - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
    - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

4. Contraception methods

Contraceptive use should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical studies.

Highly effective methods with low user dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion (e.g., bilateral tubal ligation)
- Vasectomized partner.
  - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly effective methods that are user dependent

- Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
  - Oral;
  - Intravaginal;
  - Transdermal.
- Progestogen-only hormone contraception associated with inhibition of ovulation.
  - Oral;
  - Injectable.
- Sexual abstinence.
  - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

Appendix 5 Liver safety: Suggested actions and follow-up assessments

Potential cases of drug-induced liver injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed 'tolerators,' while those who show transient liver injury but adapt are termed 'adaptors.' In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are 'susceptible' to progressive and serious liver injury, commonly referred to as DILI. Subjects who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are 'adaptors' or are 'susceptible.'

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (> 2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (i.e., AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST **OR** ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value > 2 × ULN with no evidence of hemolysis and an alkaline phosphatase value < 2 × ULN or not available.
- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values > 2 times the baseline values AND > 3 × ULN; or > 8 × ULN (whichever is smaller).
  - Pre-existing values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches > 3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the Sponsor.

The subject should return to the clinical site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected Hy's law cases, additional laboratory tests should include albumin, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (e.g., biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

Appendix 6 ECG findings of potential clinical concern

ECG findings that <u>may</u> qualify as adverse events

- Marked sinus bradycardia (rate < 40 bpm) lasting minutes
- New PR interval prolongation > 280 msec
- New prolongation of QTcF to > 480 msec (absolute) or by ≥ 60 msec from baseline
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: i.e., rate < 120 bpm
- New-onset type I second-degree (Wenckebach) AV block of > 30 seconds' duration
- Frequent PVCs, triplets, or short intervals (< 30 seconds) of consecutive ventricular complexes

ECG findings that <u>may</u> qualify as serious adverse events

- QTcF prolongation > 500 msec
- New ST-T changes suggestive of myocardial ischemia
- New-onset left bundle branch block (QRS > 120 msec)
- New-onset right bundle branch block (QRS > 120 msec)
- Symptomatic bradycardia
- Asystole:
  - In awake, symptom-free subjects in sinus rhythm, with documented periods of asystole ≥ 3.0 seconds or any escape rate < 40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free subjects with atrial fibrillation and bradycardia with one or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate > 120 bpm.
- Sustained supraventricular tachycardia (rate > 120 bpm) ('sustained' = short duration with relevant symptoms or lasting > 1 minute)
- Ventricular rhythms > 30 seconds' duration, including idioventricular rhythm (heart rate < 40 bpm), accelerated idioventricular rhythm (HR 40 bpm to < 100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR > 100 bpm [such as torsades de pointes])
- Type II second-degree (Mobitz II) AV block
- Complete (third-degree) heart block

ECG findings that qualify as serious adverse events

- Change in pattern suggestive of new myocardial infarction
- Sustained ventricular tachyarrhythmias (> 30 seconds' duration)
- Second- or third-degree AV block requiring pacemaker placement
- Asystolic pauses requiring pacemaker placement
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion
- Ventricular fibrillation/flutter
- At the discretion of the Investigator, any arrhythmia classified as an adverse experience

Note: The major events of potential clinical concern are recommended as 'alerts' or notifications from the ECG laboratory to the Investigator and Sponsor study team, and not to be considered as all inclusive of what to be reported as AEs or SAEs.

Appendix 7 Investigator signature page

BASILEA
INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

Protocol	FMGX-CP-109	Basilea product:	Fosmanogepix
Protocol title:	A Phase 1, randomized, single-center, double-blind, placebo-controlled study of fosmanogepix administered as single and multiple doses in healthy adult Chinese subjects		
Sponsor:	Basilea Pharmaceutica International Ltd, Allschwil		
Date / Version:	18 March 2025 / 3.0		
Name of Principal Investigator:			
Study site:			

I agree to the conditions relating to this study as set out in the protocol. I understand that any changes instituted by the Investigators without previous discussion with the Sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on a study subject (other than those procedures necessary for the wellbeing of the subject).

I agree to comply with International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and specifically, to obtain approval from the applicable Institutional Review Board / Independent Ethics Committee prior to study start, to allow direct access to source documents, and to allow inspection by auditors from the Sponsor and/or Health Authorities. I will ensure that the investigational product(s) supplied by the Sponsor will be used only as described in the protocol, and I acknowledge that if any other use is desired, written permission must be obtained from the Sponsor.

I acknowledge that I have read the protocol for this study, and I agree to carry out all of its terms in accordance with applicable laws and regulations.

If applicable, print name next to written signature

Written or electronic signature	**Name**	**Date**
	Principal Investigator	