CLINICAL STUDY PROTOCOL
PROTOCOL NO. F8394-101

A PHASE 1, OPEN-LABEL, 2-PART, SINGLE DOSE, CROSSOVER STUDY TO EXAMINE THE EFFECT OF FOOD AND COBICISTAT ADMINISTRATION ON THE PHARMACOKINETICS AND SAFETY OF PLIXORAFENIB IN HEALTHY PARTICIPANTS

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Version of Protocol:	Amendment 1
Date of Protocol:	03 October 2024

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation Guideline E6(R2): Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL TITLE: A Phase 1, Open-Label, 2-Part, Single Dose, Crossover Study to Examine the Effect of Food and Cobicistat Administration on the Pharmacokinetics and Safety of Plixorafenib in Healthy Participants.

PROTOCOL NUMBER: F8394-101

Signed by:
Stacie Shepherd
Signer Name: Stacie Shepherd
Signing Reason: I approve this document
Signing Time: 03-Oct-2024 | 12:45:24 PM PDT
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Stacie Peacock Shepherd, MD, PhD
Chief Medical Officer
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03-Oct-2024
Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled "A Phase 1, Open-Label, 2-Part, Single Dose, Crossover Study to Examine the Effect of Food and Cobicistat Administration on the Pharmacokinetics and Safety of Plixorafenib in Healthy Participants" in accordance with the guidelines and all applicable government regulations, including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

Signature of Principal Investigator	Date

Dr. Kristie Miller, MD
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PROTOCOL SYNOPSIS

PROTOCOL NO.: F8394-101

TITLE: A Phase 1, Open-Label, 2-Part, Single Dose, Crossover Study to Examine the Effect of Food and Cobicistat Administration on the Pharmacokinetics and Safety of Plixorafenib in Healthy Participants

STUDY PHASE: 1

STUDY SITE: 1 clinical site in the United States

OBJECTIVES:

PART A

The primary objectives for Part A of the study are as follows:

- To examine the effect of food on the single dose PK of plixorafenib administered with cobicistat.
- To examine the effect of cobicistat administration on the single dose PK of plixorafenib.
- To determine the safety of plixorafenib administered alone and with cobicistat in a single dose regimen in healthy participants.

The secondary objectives for Part A of the study are as follows:

- To characterize metabolites of plixorafenib in plasma and urine.
- To characterize the urinary excretion of plixorafenib.

The exploratory objective for Part A of the study is as follows:

- To examine the possible effect of pharmacogenomic variations on the PK of plixorafenib and/or the effect of cobicistat, including polymorphisms in P-gp, BCRP, and UGT.

PART B

Part A of this study demonstrated that co-administration of plixorafenib and cobicistat with a high fat, high caloric meal resulted in about 2-fold increase in average C_{max} and about 3-fold increase in average $AUC_{0-\infty}$, as compared to the fasted state. Since the target oncology patient population may not be able to consume high-fat and/or high-calorie meals, the effect of a low-fat meal (400 to 500 calories, with 25% from fat) and a high-fat meal (800 to 1000 calories, with ≥50% from fat) on the exposure of plixorafenib will be examined in Part B of this study, compared to the fasted state.

The primary objectives for Part B of the study are:

- To examine the effect of a high-fat and a low-fat meal versus fasted state on the single dose PK of plixorafenib administered alone.
- To examine the effect of a low-fat meal versus fasted state on the single dose PK of plixorafenib administered with cobicistat.
- To determine the safety of plixorafenib administered alone or with cobicistat (low-fat meal only) in a single dose regimen.

The exploratory objectives for Part B of the study are as follows:

- To examine the possible effects of pharmacogenomic variations on the PK of plixorafenib and/or the effect of cobicistat, including polymorphisms in P-gp, BCRP, and UGT.
- The effect of single dose administration of plixorifenib on endogenous biomarkers such as coproporphyrin may be evaluated.

STUDY DESIGN:
This is a Phase 1, open-label, 2-part, single dose, crossover, single-center study.

Part A

Part A is an open-label, randomized, single dose, 3-treatment, 3-period, crossover study designed to assess the effect of food and cobicistat administration on the PK and safety of plixorafenib in 12 healthy adult participants.

The study will consist of a screening period, 1 check-in, 3 treatment periods (with a 7-day washout between dosing in each period), and an EOS visit as illustrated in the table below:

Treatment Period	Screening	Check-in	Dosing	Confinement
1	Day -28 to -1	Day -1	Day 1	Day -1 to Day 19 (EOS)
2	N/A	N/A	Day 8	
3	N/A	N/A	Day 15	

N/A, not applicable; EOS, end of study.
There will be a 7-day washout between dosing in each treatment period.
EOS visit will be conducted on Day 19.

A screening evaluation will be performed to determine each participant's eligibility for the study approximately 28 to 1 days before the first dose. Participants eligible for participation will report to the study facility 1 day before dosing in Treatment Period 1 for check-in.

On Day 1 of Treatment Period 1, eligible participants will be randomized to 1 of 6 treatment sequences: 1:2:3, 2:3:1, 3:2:1, 2:1:3, 3:1:2, 1:3:2. On the first day of each treatment period, each participant will receive one of the following treatments according to the sequence in which he or she is randomized:

a) Treatment 1: 900 mg plixorafenib administered after overnight fast (fasted state).
b) Treatment 2: 900 mg plixorafenib + 150 mg cobicistat administered after overnight fast (fasted state).
c) Treatment 3: 900 mg plixorafenib + 150 mg cobicistat administered following a high fat, high caloric meal (fed state).

For Treatment 2 and Treatment 3, plixorafenib and cobicistat will be co-administered.

All participants will fast overnight (nothing to eat or drink except water) for at least 10 hours. Participants receiving Treatments 1 and 2 (fasted condition) will continue to fast for at least 4 hours after dosing.

Participants receiving Treatment 3 will receive a standard high fat (≥50% of the total caloric content of the meal), high caloric meal (approximately 800 to 1000 calories) for breakfast before dosing and this meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. Participants must consume the entire meal within

30 minutes of serving; the percentage of meal consumed will be documented. Dosing must occur 30 minutes (± 5 minutes) after the start of the meal. Participants receiving Treatment 3 will receive their next meal no less than 4 hours after dosing.

All study drugs will be administered orally with approximately 240 mL of room temperature water. Water (except water provided with each dosing) will be restricted 1 hour prior to and 1 hour after each study drug administration, except for consuming any fluid (ie, water, milk, juice) provided with the predose meal (treatment 3 only), but will be allowed ad libitum at all other times. Up to an additional 240 mL of water will be allowed, if necessary, to aid in swallowing the study drugs when both study drugs are administered simultaneously.

Participants will remain at the facility from check-in (Day -1) to EOS and would be able to leave the facility upon satisfactory safety review. During confinement periods, participants will receive standardized meals per the clinic's standard procedures that are scheduled at the same time in each period of the study. Participants will be discharged from the study on Day 19 (Treatment Period 3).

The duration of the study for each participant, excluding screening, will be approximately 20 days. Including screening, the total study duration for each participant will be 48 days.

Part B

Part B is an open-label, randomized, single dose, 4-treatment, 3-period, crossover study designed to assess the effect of food (either a high-fat meal or a low-fat meal) on the PK and safety of plixorafenib administered alone or with cobicistat (low-fat meal only) in 16 healthy adult participants.

This part will consist of a screening period, 1 check-in, 3 treatment periods (with a 7-day washout between dosing in each period), and an EOS visit as illustrated in the table below:

Treatment Period	Screening	Check-in	Dosing	Confinement
1	Day -28 to -1	Day -1	Day 1	Day -1 to Day 19 (EOS)
2	N/A	N/A	Day 8	
3	N/A	N/A	Day 15	

N/A, not applicable; EOS, end of study.
There will be a 7-day washout between dosing in each treatment period. EOS visit will be conducted on Day 19.

A screening evaluation will be performed to determine each participant's eligibility for the study approximately 28 to 1 days before the first dose. Participants eligible for participation will report to the study facility 1 day before dosing in Treatment Period 1 for check-in.

On Day 1 of Treatment Period 1, eligible participants will be randomized to 1 of 4 treatment sequences: A:C:D, B:D:A, D:B:C, C:A:B. On the first day of each treatment period, each participant will receive one of the following treatments according to the sequence in which he or she is randomized:

a) Treatment A: 900 mg plixorafenib administered after overnight fast (fasted state).
b) Treatment B: 900 mg plixorafenib administered following a high-fat high caloric meal (fed state-high fat meal).
c) Treatment C: 900 mg plixorafenib administered following a low-fat meal (fed state-low-fat meal).

d) Treatment D: 900 mg plixorafenib administered with 150 mg cobicistat following a low-fat meal (fed state-low-fat meal).

All participants will fast overnight (nothing to eat or drink except water) for at least 10 hours.

- Participants receiving Treatment A (fasted condition) will continue to fast for at least 4 hours after dosing.
- Participants receiving Treatment B will receive a high fat (≥50% of the total caloric content of the meal), high caloric meal (approximately 800 to 1000 calories) for breakfast before dosing and this meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively.
- Participants receiving Treatments C and D will receive a low-fat meal (approximately 400 to 500 total calories, with 25% of the total caloric content of the meal from fat) for breakfast before dosing.

All participants receiving Treatments B, C, or D must consume the entire meal within 30 minutes of serving; the percentage of meal consumed will be documented. Dosing must occur 30 minutes (± 5 minutes) after the start of the meal. Participants receiving Treatments B, C, and D will receive their next meal no less than 4 hours after dosing.

Plixorafenib will be administered orally with approximately 240 mL of room temperature water. Water (except water provided with each dosing) will be restricted 1 hour before and 1 hour after each study drug administration, except for consuming any fluid (eg, water, milk, juice) provided with the predose meal (Treatments B, C, and D) but will not be limited at other times. Up to an additional 240 mL of water will be allowed, if necessary, to aid in swallowing the study drugs when administered with cobicistat (Treatment D).

Participants will remain at the facility from check-in (Day -1) to EOS and would be able to leave the facility upon satisfactory safety review by the investigator. During confinement periods, participants will receive standardized meals per the clinic's standard procedures that are scheduled at the same time in each period of the study. Participants will be discharged from the study on Day 19 (Treatment Period 3).

The duration of the study for each participant, excluding screening, will be approximately 20 days. Including screening, the total study duration for each participant will be 48 days.

STUDY POPULATION:

Inclusion Criteria:
Each participant must meet all the following criteria to be enrolled in this study:

1. The participant is able to provide written informed consent.
2. Healthy male or non-pregnant, non-lactating female participants aged 18 to 55 years, inclusive, with a BMI of 18 kg/m^2 or greater, but less than 30 kg/m^2. The participant is considered by the investigator to be in good general health status as determined by physical examination, vital signs, temperature, medical history, no clinically significant abnormalities at investigator's discretion in laboratory and urine analyses, and with normal organ function as defined below:

- Normal renal function: creatinine clearance ≥90 mL/min.
- Normal liver enzymes and bilirubin (≤ULN).

- ECG, with QTcF interval ≤450 msec; at screening.

3. Healthy female participants must be:
    a) Documented to be surgically sterile (surgical methods inclusive of hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) or postmenopausal (amenorrhea for ≥24 months without an alternative medical cause and FSH ≥30 mIU/mL).
4. OR
    b) Using contraception, including 1 highly effective nonhormonal methods (eg, intrauterine device) in combination with a barrier contraception (eg, male or female condoms, diaphragm, spermicide, etc.) from start of plixorafenib administration until 30 days after the last plixorafenib administration, and having a negative serum or urine β-hCG pregnancy test (with a sensitivity of at least 25 mIU/mL) at screening and check-in.
5. Male participants with female partners of childbearing potential must be sterile (confirmed by documented azoospermia 90 days after the procedure) or agree to use (from check-in until 90 days after discharge) one of the following approved methods of contraception: male condom with spermicide; sterile sexual partner (males must still agree to use condom with their surgically sterile female partner if unable to provide documentation of partner's sterility); or practice abstinence (abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the participant, periodic abstinence won't be allowed); or use of an intrauterine device with spermicide by female sexual partner; a female condom with spermicide; a contraceptive sponge with spermicide; an intravaginal system; a diaphragm with spermicide; a cervical cap with spermicide; or oral, implantable, transdermal, or injectable contraceptives.
6. Male participants must refrain from sperm donation and female participants must refrain from egg donation from check-in until 90 days after discharge from the study.
7. The participant agrees to comply with all protocol requirements for the duration of the study.

Exclusion Criteria:
Participants meeting any of the following criteria will be excluded from the study:

1. The participant has a history of clinically significant drug allergy or anaphylaxis, including known hypersensitivity to any components of plixorafenib or cobicistat.
2. The participant has a history of any condition(s) or gastrointestinal surgeries, including gallbladder procedures, which might affect drug absorption, metabolism, or excretion.
3. The participant has clinical evidence or a history of clinically significant cardiovascular, respiratory, renal, hepatic, gastrointestinal, hematological, neurologic, or other chronic disease as judged by the investigator.
4. The participant has a history of psychiatric disease, a suicidal attempt, hospitalization for psychiatric disease, a period of disability due to a psychiatric disease, or administers treatment to control the condition. Psychiatric disease includes major depression, bipolar disorder, or psychosis for ≥3 months.
5. The participant has a history or other evidence of illness, test abnormalities, or any other conditions which would make the participant, in the opinion of the investigator, unsuitable for the study.

6. The participant has any history of alcoholism or drug abuse, or excessive alcohol consumption (regular alcohol intake >21 units per week for male participants and >14 units of alcohol per week for female participants) (1 unit is equal to approximately ½ pint [200 mL] of beer, 1 small glass [100 mL] of wine, or 1 measure [25 mL] of spirits) within 3 months before screening.
7. The participant has positive results on screen for drugs of abuse or alcohol (Section 6.2.3 [Other analyses]) at screening visit or Day -1.
8. The participant is a smoker or has used nicotine or nicotine-containing products (eg, snuff, nicotine pouch (eg, ZYN), nicotine patch, nicotine chewing gum, mock cigarettes, vape cigarette alternatives, or inhalers), marijuana, and cannabinoids within 1 year before the first dose of study drug.
9. The participant has donated blood in the past 90 days prior to screening or has poor peripheral venous access.
10. The participant has a diagnosis of chronic or acute liver disease, for example, auto-immune, alcoholic, or neoplastic liver disease.
11. The participant has positive serostatus for HIV, HCV, or HBV.
12. Male partners of females who are pregnant.
13. Female participant of childbearing potential who is pregnant, lactating, or planning to become pregnant within 90 days after the last dose of study drug.
14. The participant has received an investigational drug, biologic, or device within 3 months or 5 half-lives of the investigational drug (whichever is longer), before receiving study drug.
15. The participant has used any systemic medications, including vitamins and over-the-counter items, during the 14 days (or 5 times the elimination half-life of the medication, whichever is longer) before receiving study drug or will require their use during the study. Inducers and inhibitors of metabolic enzymes and/or transporters (in particular CYP3A inhibitors or inducers, P-gp, and BCRP), and herbal preparations, nutritional supplements (eg, St. John's Wort), or foods, including grapefruit juice, grapefruit/grapefruit-related citrus fruits (eg, Seville oranges, pomelos), which have been shown to produce metabolic enzyme or transporter induction or inhibition, are prohibited before 5 half-lives of the investigational drug prior to check-in (Day -1). Paracetamol ≤3000 mg/day will be allowed up to 2 consecutive days before dosing and during the outpatient phase of the study, as needed.
16. The participant has been on a diet incompatible with the on-study diet, in the opinion of the investigator or designee, within 30 days prior to the first dosing and throughout the study.
17. The participant is part of the clinical staff personnel or a family member of the clinical site staff.

STUDY TREATMENTS:
Part A

Each participant will receive the following study treatments in a crossover design:

- Treatment 1: 900 mg plixorafenib (6 × 150 mg tablets) administered after overnight fast (fasted state).

- Treatment 2: 900 mg plixorafenib (6 × 150 mg tablets) + cobicistat (1 × 150 mg tablet) administered after overnight fast (fasted state).
- Treatment 3: 900 mg plixorafenib (6 × 150 mg tablets) + cobicistat (1 × 150 mg tablet) administered following a high fat, high caloric meal (fed state).

Part B

Each participant will receive three of the following study treatments per randomization in a crossover design:

- Treatment A: 900 mg plixorafenib (6 × 150 mg tablets) administered after overnight fast (fasted state).
- Treatment B: 900 mg plixorafenib (6 × 150 mg tablets) administered following a high fat, high caloric meal (fed state-high fat meal).
- Treatment C: 900 mg plixorafenib (6 × 150 mg tablets) administered following a low-fat meal (fed state-low-fat meal).
- Treatment D: 900 mg plixorafenib (6 × 150 mg tablets) administered with 150 mg cobicistat (1 × 150 mg tablet) following a low-fat meal (fed state-low-fat meal).

STUDY PROCEDURES:

Pharmacokinetic Assessments and Endpoints:
Following administration of the study treatments, participants will have serial blood drawn (Part A and Part B) and urine (for Part A only) samples collected for determination of blood and urine concentration of plixorafenib.

Blood PK sample collection timepoints are as follows:

Study Days Timepoints	D1, D8, D15 (Dosing)	D2, D9, D16	D3, D10, D17	D4, D11, D18	D5, D12, D19
0 hour (0800)*	✓ (Predose)**	✓ (24 h)	✓ (48 h)	✓ (72 h)	✓ (96 h)
0.5 hour (0830)	✓				
1 hour (0900)	✓				
2 hour (1000)	✓				
3 hour (1100)	✓				
4 hour (1200)	✓				
6 hour (1400)	✓				
8 hour (1600)	✓	✓ (32 h)			
10 hour (1800)	✓				
12 hour (2000)	✓				

D, day; h, hours.
*Nominal clock time.
**Predose sample will be collected within 15 minutes prior to the dosing. 0 hour means dosing of study drug.

For Part A only: Prior to the predose sample, each participant will be instructed as to urine collection methods. Urine samples for the determination of plixorafenib concentrations will be collected at selected time intervals, as specified in the table below. All participants will be asked to void their bladder within 45 minutes prior to dosing. After administration of plixorafenib, all urine will be collected completely per each collection interval. Urine portions will be pooled per

participant within this collection interval. Just prior to the end of the sampling interval, participants will be encouraged to void their bladder again to complete the collection. The start and end times of the urine collection will be recorded. Three aliquot (5 mL each) will be obtained from each pooled urine sample: 1 for the quantification of plixorafenib, 1 for the metabolite analysis, and 1 as a back-up. Instructions for sample preparation and storage can be found in the study lab manual.

Urine samples for the quantitation of plixorafenib, collection timepoints are as follows:

Study Days Timepoints	**D1, D8, D15 (Dosing Day)**	**D2, D9, D16**
Predose*	✓	
0-4 hours	✓	
4-8 hours	✓	
8-12 hours	✓	
12-24 hours		✓
24-48 hours		✓

D, days.
*45 minutes prior to dosing.

The following PK parameters will be calculated using model-independent approaches (NCA) from plixorafenib individual plasma concentrations, whenever practical.

Plasma Parameters (Part A and Part B)

- Area under the plasma concentration versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}).
- AUC from time 0 extrapolated to infinity (AUC_{0-inf}).
- Maximum observed plasma concentration (C_{max}).
- Time to maximum observed plasma concentration (T_{max}).
- Terminal elimination rate constant (K_{el}).
- Terminal phase half-life ($t_{1/2}$).
- Apparent oral clearance (CL/F).
- Apparent volume of distribution (V_d/F).
- Terminal rate constant calculated from the terminal slope of the log-linear regression of concentration with time (λ_z).
- Calculated lag time: time taken for the drug to appear in the systemic circulation following administration, when applicable (T_{lag}).

Urine Parameters (Part A Only)

- Cumulative amount of plixorafenib excreted in urine, calculated as the sum of the product of urine concentration and urine volume (A_e).
- Percent of dose excreted in urine in 48 hours calculated as $100*A_e/Dose$.

Blood and urine samples may be used to evaluate the metabolic profile of plixorafenib and the results will be described separately.

Blood and/or plasma samples may be used to measure endogenous biomarkers, such as coproporphyrin I, to assess possible transporters inhibition.

Pharmacogenomics:
A blood sample for pharmacogenomic evaluation will be collected at screening. Possible effects of pharmacogenomic variations on the PK of plixorafenib and/or the effect of cobicistat, including but not limited to polymorphisms in P-gp, BCRP, and UGT, will be examined, if feasible.

Safety Assessments and Endpoints:
Safety will be assessed by the following: monitoring and recording of AEs; clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECG results, and physical examination findings.

STATISTICAL ANALYSIS PLANS:

Sample Size:
The number of participants is based on clinical and practical considerations and not on a formal statistical power calculation. The total sample size of 12 participants in Part A and 16 participants in Part B is considered sufficient for the objectives of the study.

Analysis Sets:
The PK population will include participants who receive at least 1 dose of plixorafenib with or without cobicistat and have sufficient concentration data to support accurate estimation of at least 1 PK parameter. Participants who experience vomiting within 2 times the median T_{max} after study drug dosing will be excluded from the PK analysis.

The safety population will include all participants who receive at least 1 dose of plixorafenib with or without cobicistat.

Pharmacokinetic Analyses:
Individual plasma concentration and time deviation data will be presented in a data listing. Plasma concentration data will be summarized by time point for each treatment (plixorafenib alone in fasted state, plixorafenib + cobicistat in fasted state or plixorafenib + cobicistat in fed state) using the following descriptive statistics: number of participants, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. Individual and mean plasma concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales.

The PK parameters of plixorafenib will be determined using noncompartmental methods based on the actual sampling times. All parameters will be calculated using Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.3 or higher. The individual PK parameters will be presented in data listings and summarized by treatment using the following descriptive statistics: number of participants, mean, SD, CV, median, minimum, and maximum. Geometric means will be included for AUC_{0-t}, AUC_{0-inf}, and C_{max}.

If warranted, a linear mixed model with treatment as a fixed effect and participant as a random effect will be performed on the natural log-transformed values of AUC_{0-t}, AUC_{0-inf}, and C_{max} to assess the effect of cobicistat and/or food on the PK of plixorafenib. The geometric least squares means and corresponding 90% CIs will be computed for AUC_{0-t}, AUC_{0-inf}, and C_{max} of

plixorafenib administered alone (Reference Treatment) versus plixorafenib with cobicistat and/or food (Test Treatments) by taking the antilog of the least squares means from the linear mixed-effect model on the natural logarithms of the corresponding PK parameters. A 90% CI for the ratio will be constructed as the antilog of the confidence limits of the mean difference.

It will be concluded that there is no relevant interaction of cobicistat or food on plixorafenib if the 90% CIs for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} ratios of the Reference Treatment to the Test Treatments are completely contained within the (80%, 125%) interval.

Safety Analyses:
Adverse events will be coded by preferred term and system organ class using the latest version of MedDRA. All AE data will be presented in a data listing. TEAEs will be summarized by treatment and overall, as well as by severity, seriousness, and relationship to study drug. SAEs and AEs leading to discontinuation of study drug will also be presented in the data listings and summarized by treatment and overall.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of participants, mean, SD, median, minimum, and maximum. Physical examination findings will be presented in a data listing.

Other Analyses: Evaluation of the metabolic profile of plixorafenib in plasma (Parts A and B) and urine (Part A only) will be conducted and the results will be reported separately.

Possible effects of pharmacogenomic variations on the PK of plixorafenib and/or the effect of cobicistat, including but not limited to polymorphisms in P-gp, BCRP, and UGT, will be examined, if feasible.

DATE OF PROTOCOL: Amendment 1, 03 October 2024

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 Plixorafenib

Plixorafenib (also known as FORE8394 and formerly known as PLX8394) is a first-in-class selective RAF murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor that blocks mutant BRAF in tumor cells without activating the MAPK pathway. Plixorafenib has nonclinical and clinical activity against both monomeric V600 mutations and dimeric non-V600 BRAF alterations, including BRAF fusions and deletion mutations.

Plixorafenib is a next-generation, orally available, small-molecule, selective potent inhibitor of activated BRAF (Class 1 and 2, including fusions). Unlike first-generation RAF inhibitors, plixorafenib specifically disrupts BRAF-containing dimers and does not appear to induce paradoxical activation of the MAPK pathway. Therefore, plixorafenib as a "paradox breaker" may provide both improved safety and more durable efficacy than first- and second-generation RAF inhibitors. Preclinical and clinical findings support that plixorafenib does not have the tumor activating potential observed with the first- and second-generation compounds.

Plixorafenib as a BRAF inhibitor presents a notable differential regulation of major pathways, including MAPK signaling, apoptosis, cell cycle, or developmental signaling pathways. Combinatorial treatments of plixorafenib with MCL-1 and Notch modulators show a better effect than single agent treatments, suggesting additional pathways could be further exploited in novel efficient combinatorial treatment protocols with plixorafenib (Koumaki 2021).

Plixorafenib overcomes several known mechanisms of resistance to first-generation BRAF inhibitors when tested in relevant vemurafenib resistant cell models. The in vivo anti-tumor activity of plixorafenib and PK-PD relationship have been characterized in several BRAF-V600E xenograft models. To date, no specific concerns about safety have emerged from safety pharmacology evaluations of plixorafenib.

Nonclinical Summary:

Pharmacology: Plixorafenib inhibits the mutated BRAF kinases including Class 1 BRAF-V600E and V600K and Class 2 BRAF K601E, T599I, and G469A with single-digit nM IC_{50} values and to a lesser extent wild type BRAF and CRAF, while having minimal effects on the activities of >260 other kinases. Unlike all first-generation BRAF inhibitors, plixorafenib does not induce RAF dimer formation. In nonclinical squamous cell tumor models, the first-generation- RAF inhibitor vemurafenib stimulated in vitro and in vivo growth and induced the expression of both downstream MAPK pathway response genes and upstream EGFR ligands. In contrast, plixorafenib had no effect. By dissociating MAPK pathway inhibition from pathway activation, plixorafenib may provide improved clinical outcomes with fewer side effects or the need for co-administration of a MEK inhibitor related to unwanted activation. No specific concerns have emerged from safety pharmacology evaluations of plixorafenib.

Pharmacokinetics: Plixorafenib is a metabolically stable drug that displays low aqueous solubility, high permeability, and extensive plasma protein binding. In vivo testing in multiple species has shown that plixorafenib is absorbed within 3 to 5 hours following oral administration. Following a single oral dose of plixorafenib in Sprague Dawley rats, wide tissue distribution was observed, with low CNS to plasma ratio.

In vitro data suggest that the metabolism of plixorafenib is mediated primarily by the cytochrome P450 (CYP)3A isoenzyme. Based on in vitro transporter substrate and inhibition studies, plixorafenib is a substrate of P-gp, and BCRP, and an inhibitor of P-gp, BCRP, BSEP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2K, MRP3, and MRP4. Cobicistat is an inhibitor of CYP3A and CYP2D6, and inhibits the following transporters: P-gp, BCRP, OATP1B1, and OATP1B3. In an in-vitro experiment in human liver cells, the addition of cobicistat completely blocked the metabolism of plixorafenib. Plixorafenib neither inhibits (direct or time-dependent) nor induces CYP enzymes in vitro.

Toxicology: In the GLP repeat-dose 28-day toxicology studies in Sprague Dawley rats and beagle dogs, the NOAELs were determined to be 450 mg/kg/day and 300 mg/kg/day, respectively. No adverse effects thought to be related to plixorafenib treatment were identified. A non-adverse slight increase in the severity of renal hyaline droplets in the kidneys was observed in male rats at ≥150 mg/kg/day; however, this kidney change was not relevant to humans. Non-adverse plixorafenib-related microscopic observations were noted in the bone marrow (minimal to mild coagulative necrosis) and liver (minimal single cell necrosis) of male dogs at 300 mg/kg/day. Exacerbation of spontaneous polyarteritis, not considered a plixorafenib-related effect, was also observed in dogs at ≥100 mg/kg/day. Importantly, no ophthalmologic findings were identified in either species. In genotoxicity studies performed under GLP conditions, plixorafenib was found to be non-mutagenic and non-clastogenic (Fore Biotherapeutics 2023).

Clinical Summary:

As of 29 January 2024, a total of 174 participants have been exposed to study drug in clinical trials. Two studies have been completed, Study PLX120-01 and Study PLX120-04. One study (PLX120-03) is ongoing with the enrollment complete, and 1 study (F8394-201) is actively enrolling.

Study PLX120-04 was a Phase 1, open-label, 2-part study to evaluate the PK and safety of single ascending doses of plixorafenib (previous HME formulation) and to assess the effect of cobicistat (a pharmacoenhancer) on the PK of plixorafenib in healthy participants. In Study PLX120-04, plixorafenib showed linear PK when administered as single ascending doses under fasted conditions over the studied dose range of 150 to 900 mg. Cobicistat co-administration increased plixorafenib exposure. Compared with plixorafenib administered alone, the mean AUC from $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ increased 2.6-fold (300 mg level) and 3.8-fold (900 mg level), and the mean C_{max} increased 1.8-fold (300 mg level) and 2.7-fold (900 mg level). Single doses of plixorafenib were well tolerated when administered either alone or in combination with cobicistat.

Study PLX120-03 is an ongoing, Phase 1/2a, open-label, single-arm clinical trial designed to evaluate the safety, PK, pharmacodynamics, and preliminary efficacy of plixorafenib in adult and

pediatric participants with advanced unresectable solid or CNS tumors harboring BRAF alterations. Preliminary PK data are available from 84 adult participants through 31 October 2022. When plixorafenib was administered alone, a modest increase in exposure was observed between the 450 mg BID and the 900 mg BID dose groups. In addition, slight accumulation was observed upon BID dosing for at least 15 days. Administration of plixorafenib with cobicistat resulted in approximately 2- to 3-fold increase in systemic exposure compared to plixorafenib alone. Increases in dose resulted in increases in plixorafenib exposure up to 900 mg BID with no additional increase in exposure observed at the 1350 mg and 1800 mg BID dose. Exposure parameters for the SDD formulation suggest comparable exposure for the HME and the SDD formulations. Overall, the high variability in the data, along with the small number of participants and limited sampling scheme, may have impacted the PK assessments. Plixorafenib has demonstrated an acceptable safety profile. Cutaneous events with potential to develop into treatment-emergent malignancies in the skin and other epithelial tissues, that have been observed with other first-generation inhibitors, have not been observed with plixorafenib, supporting the lack of paradoxical activation. Preliminary efficacy from the ongoing PLX120-03 Phase 1/2a study supports long term tolerability and a promising signal of clinical benefit with 10 participants receiving study treatment for ≥2 years (range: 2.4 to 7.6 years) and responses observed across advanced solid tumors harboring V600 or non-V600 BRAF alterations.

The F8394-201 study is a Phase 2 global multicenter master protocol to assess the efficacy and safety of plixorafenib in participants 10 years of age or older with advanced cancer harboring eligible BRAF alterations. The potential benefits of plixorafenib treatment include durable single-agent anti-tumor effects against BRAF-altered tumors in both adults and children with advanced malignancies or LCH and a reduced risk of paradoxical MAPK pathway activation.

Cobicistat is a PK booster administered with plixorafenib. In clinical studies, cobicistat resulted in about a 2- to 3-fold increase in systemic exposure of plixorafenib compared to plixorafenib alone. Cobicistat decreases estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. Cobicistat may have possible or significant known interactions with concomitant medications, foods, or herbal remedies. The potential for interactions should be considered when cobicistat is administered and steps taken to prevent or manage these possible and known significant drug interactions. Refer to the prescribing information of cobicistat for further information.

Further information on the study drug can be found in the Investigator's Brochure (Fore Biotherapeutics 2023).

1.1.2 Cobicistat

Cobicistat is a mechanism-based inhibitor of the CYP3A isoenzyme family that is approved and marketed as a PK enhancer of HIV-1 protease inhibitors in adults (Tybost® 2021). Cobicistat is also an inhibitor of several transporters that include P-gp, BCRP, OATP1B1, and OATP1B3. The most common Grade ≥2 ADRs observed with cobicistat (in combination with atazanavir) are jaundice and rash. Cobicistat is contraindicated with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect. The plasma concentration of drugs that are primarily metabolized by CYP3A or CYP2D6,

or are substrates of P-gp, BCRP, OATP1B1, or OATP1B3, may be increased if those drugs are coadministered with cobicistat.

As plixorafenib is a substrate of P-gp and in vitro data suggest that the metabolism of plixorafenib is mediated primarily by CYP3A, cobicistat was evaluated as a possible booster of plixorafenib exposure. In an in vitro study, the addition of cobicistat completely blocked the metabolism of plixorafenib by CYP3A4. In an in vitro blood-brain barrier model, cobicistat 5 μM increased the apical to basolateral permeability coefficient value (Papp) of plixorafenib 13-fold. In clinical studies in participants with advanced cancer (PLX120-03), administration of plixorafenib with cobicistat resulted in about 2- to 3-fold increase in systemic exposure compared to plixorafenib alone.

Cobicistat exposures were not affected by food. (Prezcobix® 2023).

1.2 RATIONALE FOR STUDY

This study will assess the effect of food on the single dose PK of plixorafenib administered with cobicistat in accordance with the FDA guidance for industry on assessing the effects of food on drugs in INDs and NDAs — Clinical Pharmacology Considerations (DHHS 2022).

This study is designed in accordance with the US FDA Guidance for Industry, Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications (DHHS 2017) to assess the effects of cobicistat administration on the single dose PK of plixorafenib.

For Part A, the effect of food on the single dose PK of plixorafenib (900 mg) administered concomitantly with cobicistat, will be evaluated as participants in other current studies evaluating plixorafenib are instructed to take their study treatment on an empty stomach (fasting for 2 hours before and one hour after dosing) as the effect of food on the PK of plixorafenib has not been formally evaluated yet. Characterizing the food effect may allow more flexibility in plixorafenib dosing. This study will investigate the effect of cobicistat on the PK and safety of plixorafenib using the SDD formulation.

Metabolism and urinary excretion will also be evaluated in this study to assess the urinary excretion of plixorafenib and examine its metabolic fate.

Plixorafenib is being administered with cobicistat in this study as in vitro data suggest that the metabolism of plixorafenib is mediated primarily by the CYP3A isoenzyme. In a clinical study (Study PLX120-04), cobicistat co-administration increased plixorafenib exposure. Compared with plixorafenib administered alone as the HME formulation, the mean AUC from $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ increased 2.6-fold (300 mg level) and 3.8-fold (900 mg level), and the mean C_{max} increased 1.8-fold (300 mg level) and 2.7-fold (900 mg level). Single doses of plixorafenib were well tolerated when administered either alone or in combination with cobicistat.

Part A of this study demonstrated that co-administration of plixorafenib and cobicistat with a high fat, high caloric meal resulted in about 2-fold increase in average C_{max} and about 3-fold increase in average $AUC_{0\text{-}\infty}$, as compared to the fasted state. Since the target oncology patient population may not be able to consume high-fat and/or high-calorie meals, the effect of a low-fat

meal (400 to 500 calories, with 25% from fat) and a high-fat meal (800 to 1000 calories, with ≥50% from fat) on the exposure of plixorafenib will be examined in Part B of this study, compared to the fasted state.

1.3 RATIONALE FOR DOSE SELECTION

Nonclinical and clinical data to date indicate that plixorafenib has an acceptable safety profile.

In the PLX120-03 Phase 1/2a study evaluating multiple dosing (ranging from plixorafenib 900-3600 mg/day with and without cobicistat; N=113) administered until disease progression in participants with advanced cancers, plixorafenib 900 mg QD with cobicistat 150 mg QD was selected as the RP2D based upon the overall safety, PK, PD, and efficacy in BRAF-altered tumors. DLTs consisted of transient Grade 3 laboratory abnormalities in transaminases and/or bilirubin and occurred in 6 participants (none meeting Hy's law). No DLTs were observed with plixorafenib ≤1200 mg/day, with or without cobicistat, including at the RP2D of plixorafenib 900 mg QD co-administered with cobicistat 150 mg QD.

Transient increases in ALT, AST, and bilirubin have been observed in participants with advanced malignancies receiving plixorafenib until disease progression. These changes can be monitored with routine laboratory studies and are manageable with dose interruptions and reductions. Participants have continued to tolerate treatment following these events, and no cases of hepatic failure have been reported. To mitigate this risk, liver chemistry assessments are closely monitored in all clinical studies (Fore Biotherapeutics 2023). The single dose of plixorafenib with or without cobicistat utilized in this Phase 1 study are in line with those evaluated in the PLX120-04 Phase 1 study in healthy participants (plixorafenib 150 to 900 mg; including assessing the effect of cobicistat) that encompassed a clinically relevant exposure and demonstrated an acceptable safety profile.

2. STUDY OBJECTIVES

The objectives of Part A and Part B are provided below.

2.1 PRIMARY OBJECTIVE

The primary objectives for Part A of the study are as follows:

- To examine the effect of food on the single dose PK of plixorafenib administered with cobicistat.
- To examine the effect of cobicistat administration on the single dose PK of plixorafenib.
- To determine the safety of plixorafenib administered alone and with cobicistat in a single dose regimen in healthy participants.

The primary objectives for Part B of the study are:

- To examine the effect of a high-fat and a low-fat meal versus fasted state on the single dose PK of plixorafenib administered alone.
- To examine the effect of a low-fat meal versus fasted state on the single dose PK of plixorafenib administered with cobicistat.
- To determine the safety of plixorafenib administered alone or with cobicistat (low-fat meal only) in a single dose regimen.

2.2 SECONDARY OBJECTIVES

The secondary objectives for Part A of the study are as follows:

- To characterize metabolites of plixorafenib in plasma and urine.
- To characterize the urinary excretion of plixorafenib.

There are no secondary objectives for Part B of the study.

2.3 EXPLORATORY OBJECTIVE

The exploratory objective for Part A and Part B of the study is as follows:

- To examine the possible effect of pharmacogenomic variations on the PK of plixorafenib and/or the effect of cobicistat, including polymorphisms in P-gp, BCRP, and UGT.

The exploratory objective for Part B of the study is as follows:

- The effect of single dose administration of plixorifenib on endogenous biomarkers such as coproporphyrin may be evaluated.

3. STUDY DESIGN

This is a Phase 1, open-label, 2-part, single dose, crossover, single-center study.

3.1 PART A

Part A is an open-label, randomized, single dose, 3-treatment, 3-period, crossover study designed to assess the effect of food and cobicistat administration on the PK and safety of plixorafenib in 12 healthy adult participants.

The study will consist of a screening period, 1 check-in, 3 treatment periods (with a 7-day washout between dosing in each period), and an EOS visit as illustrated in Table 3-1:

Table 3-1 Study Description for Part A

Treatment Period	Screening	Check-in	Dosing	Confinement
1	Day -28 to -1	Day -1	Day 1	Day -1 to Day 19 (EOS)
2	N/A	N/A	Day 8	
3	N/A	N/A	Day 15	

N/A, not applicable; EOS, end of study

There will be a 7-day washout between dosing in each treatment period.
EOS visit will be conducted on Day 19.

A screening evaluation will be performed to determine each participant's eligibility for the study approximately 28 to 1 days before the first dose. Participants eligible for participation will report to the study facility 1 day before dosing in Treatment Period 1 for check-in.

On Day 1 of Treatment Period 1, eligible participants will be randomized to 1 of 6 treatment sequences: 1:2:3, 2:3:1, 3:2:1, 2:1:3, 3:1:2, 1:3:2. On the first day of each treatment period, each participant will receive one of the following treatments according to the sequence in which he or she is randomized:

- Treatment 1: 900 mg plixorafenib administered after overnight fast (fasted state).
- Treatment 2: 900 mg plixorafenib + 150 mg cobicistat administered after overnight fast (fasted state).
- Treatment 3: 900 mg plixorafenib + 150 mg cobicistat administered following a high fat, high caloric meal (fed state).

For Treatment 2 and Treatment 3, plixorafenib and cobicistat will be co-administered.

All participants will fast overnight (nothing to eat or drink except water) for at least 10 hours. Participants receiving Treatments 1 and 2 (fasted condition) will continue to fast for at least 4 hours after dosing.

Participants receiving Treatment 3 will receive a standard high fat (≥50% of the total caloric content of the meal), high caloric meal (approximately 800 to 1000 calories) for breakfast before dosing and this meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively (DHHS 2022). Participants must consume the entire meal within 30 minutes of serving; the percentage of meal consumed will be documented. Dosing must occur 30 minutes (± 5 minutes) after the start of the meal. Participants receiving Treatment 3 will receive their next meal no less than 4 hours after dosing.

All study drugs will be administered orally with approximately 240 mL of room temperature water. Water (except water provided with each dosing) will be restricted 1 hour prior to and 1 hour after each study drug administration, except for any fluid (ie, water, milk, juice) provided with the predose meal (Treatment 3 only), but will be allowed ad libitum at all other times. Up to an additional 240 mL of water will be allowed, if necessary, to aid in swallowing the study drugs when both study drugs are administered simultaneously.

Participants will remain at the facility from check-in (Day -1) to EOS and would be able to leave the facility upon satisfactory safety review. During confinement, participants will receive standardized meals per the clinic's standard procedures that are scheduled at the same time in each period of the study. Participants will be discharged from the study on Day 19 (Treatment Period 3).

The duration of the study for each participant, excluding screening period, will be approximately 20 days. Including screening period, the total study duration for each participant will be 48 days.

3.2 PART B

Part B is an open-label, randomized, single dose, 4-treatment, 3-period, crossover study designed to assess the effect of food (either a high-fat meal or a low-fat meal) on the PK and safety of plixorafenib administered alone or with cobicistat (low-fat meal only) in 16 healthy adult participants.

This part will consist of a screening period, 1 check-in, 3 treatment periods (with a 7-day washout between dosing in each period), and an EOS visit as illustrated in Table 3-2:

Table 3-2 Study Description for Part B

Treatment Period	Screening	Check-in	Dosing	Confinement
1	Day -28 to -1	Day -1	Day 1	Day -1 to Day 19 (EOS)
2	N/A	N/A	Day 8	
3	N/A	N/A	Day 15	

N/A, not applicable; EOS, end of study.
There will be a 7-day washout between dosing in each treatment period. EOS visit will be conducted on Day 19.

A screening evaluation will be performed to determine each participant's eligibility for the study approximately 28 to 1 days before the first dose. Participants eligible for participation will report to the study facility 1 day before dosing in Treatment Period 1 for check-in.

On Day 1 of Treatment Period 1, eligible participants will be randomized to 1 of 4 treatment sequences: A:C:D, B:D:A, D:B:C, C:A:B. On the first day of each treatment period, each participant will receive one of the following treatments according to the sequence in which he or she is randomized:

a) Treatment A: 900 mg plixorafenib administered after overnight fast (fasted state).

b) Treatment B: 900 mg plixorafenib administered following a high-fat high caloric meal (fed state-high fat meal).

c) Treatment C: 900 mg plixorafenib administered following a low-fat meal (fed state-low-fat meal).

d) Treatment D: 900 mg plixorafenib administered with 150 mg cobicistat following a low-fat meal (fed state-low-fat meal).

All participants will fast overnight (nothing to eat or drink except water) for at least 10 hours.

- Participants receiving Treatment A (fasted condition) will continue to fast for at least 4 hours after dosing.

- Participants receiving Treatment B will receive a high fat (≥50% of the total caloric content of the meal), high caloric meal (approximately 800 to 1000 calories) for breakfast before dosing and this meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively.

- Participants receiving Treatments C and D will receive a low-fat meal (approximately 400 to 500 total calories, with 25% of the total caloric content of the meal from fat) for breakfast before dosing.

All participants receiving Treatments B, C, or D must consume the entire meal within 30 minutes of serving; the percentage of meal consumed will be documented. Dosing must occur 30 minutes (± 5 minutes) after the start of the meal. Participants receiving Treatments B, C, and D will receive their next meal no less than 4 hours after dosing.

Plixorafenib will be administered orally with approximately 240 mL of room temperature water. Water (except water provided with each dosing) will be restricted 1 hour before and 1 hour after each study drug administration, except for consuming any fluid (eg, water, milk, juice) provided with the predose meal (Treatments B, C, and D) but will not be limited at other times. Up to an additional 240 mL of water will be allowed, if necessary, to aid in swallowing the study drugs when administered with cobicistat (Treatment D).

Participants will remain at the facility from check-in (Day -1) to EOS and would be able to leave the facility upon satisfactory safety review by the investigator. During confinement periods, participants will receive standardized meals per the clinic's standard procedures that are scheduled at the same time in each period of the study. Participants will be discharged from the study on Day 19 (Treatment Period 3).

The duration of the study for each participant, excluding screening, will be approximately 20 days. Including screening, the total study duration for each participant will be 48 days.

3.3 SCHEDULE OF EVENTS

3.3.1 Schedule of Events for Study Part A

	Phase	Screening	Check-in	Treatment Period 1					Treatment Period 2					Treatment Period 3				
Procedure[a]	**Day/Treatment**	**D–28 to –1**	**Day -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**D9**	**D10**	**D11**	**D12**	**D15**	**D16**	**D17**	**D18**	**D19/EOS**
Admission to clinic			X															
Discharge from the clinic/study																		X
Informed consent		X																
Demographics		X																
Serology[b]		X																
Serum FSH[c]		X																
Inclusion/exclusion criteria		X	X															
Medical history		X	X															
Height, weight, and BMI[d]		X	X	X					X					X				X
Physical examination[e]		X	X	X					X					X				X
Vital sign measurements[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[g]		X		X					X					X				X
Clinical laboratory testing[h]		X	X				X					X					X	X
Urinalysis[h]		X	X				X					X					X	X
Urine drug/alcohol/cotinine screen[i]		X	X															
Pregnancy test[j]		X	X															X
Sample for pharmacogenomics		X																
Study drug administration[k]				X					X					X				
PK sample collection[l]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK sample collection[m]				X	X				X	X				X	X			
Adverse events[n]		X																
Prior/concomitant medications [o]		X																

Abbreviations: AEs, adverse events; BCRP, breast cancer resistance protein; BMI, body mass index; D, day; ECG, electrocardiogram; EOS, end of study; FSH, follicle-stimulating hormone; PD, pharmacodynamic; P-gp, P-glycoprotein; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia's formula

Notes:

a) When procedures are scheduled for the same timepoint ECG should be performed first, followed by vital sign assessment, urine collection, meal, blood collection, and dose (in that order).
b) A complete list of serology assessments is provided in Section 6.2.3.
c) Females only. Further details are provided in Section 6.2.3.

d) Height and weight will be measured, and BMI calculated at screening only. Only weight will be measured at check-in, dosing, and EOS.
e) A full physical examination will be performed at screening and check-in. A symptom-driven physical examination may be performed at other times, at the investigator's or designee's discretion. Further details are provided in Section 6.2.6.
f) Further details on vital signs (respiratory rate, body temperature, pulse rate, and blood pressure) measurements are provided in Section 6.2.4.
g) ECG should be recorded at screening, predose within 2 hours on each dosing day, and at EOS. Further details on ECG recordings are provided in Section 6.2.5.
h) Clinical laboratory testing will occur at screening, check-in, 3 days from dosing (Day 4, 11, 18), and at EOS. If any concerning trends are seen during study, the investigator can order additional testing for safety on PRN basis. Further details on clinical laboratory assessments, including a complete list of assessments, are provided in Section 6.2.3.
i) Further details are provided in Section 6.2.3.
j) Urine pregnancy test to be done at screening. Serum pregnancy test to be done at check-in, and at EOS.
k) Further details on dosing of study treatments are provided in Section 5.1.
l) Further details on the collection of blood samples for PK analysis are provided in Section 6.1 and in Table 6-1.
m) Further details on the collection of urine samples for PK analysis are provided in Section 6.1 and in Table 6-2.
n) Further details on collection and reporting of AEs are provided in Section 6.2.
o) Information regarding prior medications taken by the participant within the 30 days before signing the ICF will be recorded in the participant's eCRF. Details regarding prior and concomitant medications are provided in Section 5.5.1.

3.3.2 Schedule of Events for Study Part B

	Phase	Screening	Check-in	Treatment Period 1					Treatment Period 2					Treatment Period 3				
Procedure[a]	**Day/Treatment**	**D–28 to –1**	**Day -1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**D9**	**D10**	**D11**	**D12**	**D15**	**D16**	**D17**	**D18**	**D19/EOS**
Admission to clinic			X															
Discharge from the clinic/study																		X
Informed consent		X																
Demographics		X																
Serology[b]		X																
Serum FSH[c]		X																
Inclusion/exclusion criteria		X	X															
Medical history		X	X															
Height, weight, and BMI[d]		X	X	X					X					X				X
Physical examination[e]		X	X	X					X					X				X
Vital sign measurements[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[g]		X		X					X					X				X
Clinical laboratory testing[h]		X	X	X			X		X			X		X			X	X
Urinalysis[h]		X	X	X			X		X			X		X			X	X
Urine drug/alcohol/cotinine screen[i]		X	X															
Pregnancy test[j]		X	X															X
Sample for pharmacogenomics		X																
Study drug administration[k]				X					X					X				
PK sample collection[l]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[m]		X																
Prior/concomitant medications [n]		X																

Abbreviations: AEs, adverse events; BCRP, breast cancer resistance protein; BMI, body mass index; D, day; ECG, electrocardiogram; EOS, end of study; FSH, follicle-stimulating hormone; PD, pharmacodynamic; P-gp, P-glycoprotein; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia's formula

Notes:

a) When procedures are scheduled for the same timepoint ECG should be performed first, followed by vital sign assessment, urine collection, meal, blood collection, and dose (in that order).
b) A complete list of serology assessments is provided in Section 6.2.3.
c) Females only. Further details are provided in Section 6.2.3.
d) Height and weight will be measured, and BMI calculated at screening only. Only weight will be measured at check-in, dosing, and EOS.
e) A full physical examination will be performed at screening and check-in. A symptom-driven physical examination may be performed at other times, at the investigator's or designee's discretion. Further details are provided in Section 6.2.6.
f) Further details on vital signs (respiratory rate, body temperature, pulse rate, and blood pressure) measurements are provided in Section 6.2.4.

g) ECG should be recorded at screening, predose within 2 hours on each dosing day, and at EOS. Further details on ECG recordings are provided in Section 6.2.5.
h) Clinical laboratory testing will occur at screening, check-in, predose within 2 hours on each dosing day, 3 days from dosing (Day 4, 11, 18), and at EOS. If any concerning trends are seen during study, the investigator can order additional testing for safety on PRN basis. Further details on clinical laboratory assessments, including a complete list of assessments, are provided in Section 6.2.3.
i) Further details are provided in Section 6.2.3.
j) Urine pregnancy test to be done at screening. Serum pregnancy test to be done at check-in, and at EOS.
k) Further details on dosing of study treatments are provided in Section 5.1.
l) Further details on the collection of blood samples for PK analysis are provided in Section 6.1 and in Table 6-1.
m) Further details on collection and reporting of AEs are provided in Section 6.2.
n) Information regarding prior medications taken by the participant within the 30 days before signing the ICF will be recorded in the participant's eCRF. Details regarding prior and concomitant medications are provided in Section 5.5.1.

4. STUDY POPULATION

Approximately 12 participants in Part A and 16 participants in Part B will be enrolled at a single center in the United States.

4.1 INCLUSION CRITERIA

Each participant must meet all the following criteria to be enrolled in this study:

1. The participant is able to provide written informed consent.

2. Healthy male or non-pregnant, non-lactating female participants aged 18 to 55 years, inclusive, with a BMI of 18 kg/m^2 or greater, but less than 30 kg/m^2. The participant is considered by the investigator to be in good general health status as determined by physical examination, vital signs, temperature, medical history, no clinically significant abnormalities at investigator's discretion in laboratory and urine analyses and with normal organ function as defined below:

   - Normal renal function: creatinine clearance ≥90 mL/min
   - Normal liver enzymes and bilirubin (≤ULN)
   - ECG, with QTcF interval ≤450 msec; at screening.

3. Healthy female participants must be:

   a) Documented to be surgically sterile (surgical methods inclusive of hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) or postmenopausal (amenorrhea for ≥24 months without an alternative medical cause and FSH ≥30 mIU/mL).
   OR
   b) Using contraception, including 1 highly effective nonhormonal methods (eg, intrauterine device) in combination with a barrier contraception (eg, male or female condoms, diaphragm, spermicide, etc.) from start of plixorafenib administration until 30 days after the last plixorafenib administration, and having a negative serum or urine β-hCG pregnancy test (with a sensitivity of at least 25 mIU/mL) at screening and check-in.

4. Male participants with female partners of childbearing potential must be sterile (confirmed by documented azoospermia 90 days after the procedure) or agree to use (from check-in until 90 days after discharge) one of the following approved methods of contraception: male condom with spermicide; sterile sexual partner (males must still agree to use condom with their surgically sterile female partner if unable to provide documentation of partner's sterility); or practice abstinence (abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the participant, periodic abstinence won't be allowed); or use of an intrauterine device with spermicide by female sexual partner; a female condom with spermicide; a contraceptive sponge with spermicide; an intravaginal system; a diaphragm with spermicide; a cervical cap with spermicide; or oral, implantable, transdermal, or injectable contraceptives.

5. Male participants must refrain from sperm donation and female participants must refrain from egg donation from check-in until 90 days after discharge from the study.

6. The participant agrees to comply with all protocol requirements for the duration of the study.

4.2 EXCLUSION CRITERIA

Participants meeting any of the following criteria will be excluded from the study:

1. The participant has a history of clinically significant drug allergy or anaphylaxis, including known hypersensitivity to any components of plixorafenib or cobicistat.

2. The participant has a history of any condition(s) or gastrointestinal surgeries, including gallbladder procedures, which might affect drug absorption, metabolism, or excretion.

3. The participant has clinical evidence or a history of clinically significant cardiovascular, respiratory, renal, hepatic, gastrointestinal, hematological, neurologic, or other chronic disease as judged by the investigator.

4. The participant has a history of psychiatric disease, a suicidal attempt, hospitalization for psychiatric disease, a period of disability due to a psychiatric disease, or administers treatment to control the condition. Psychiatric disease includes major depression, bipolar disorder, or psychosis for ≥3 months.

5. The participant has a history or other evidence of illness, test abnormalities, or any other conditions which would make the participant, in the opinion of the investigator, unsuitable for the study.

6. The participant has any history of alcoholism or drug abuse, or excessive alcohol consumption (regular alcohol intake >21 units per week for male participants and >14 units of alcohol per week for female participants) (1 unit is equal to approximately ½ pint [200 mL] of beer, 1 small glass [100 mL] of wine, or 1 measure [25 mL] of spirits) within 3 months before screening.

7. The participant has positive results on screen for drugs of abuse or alcohol (Section 6.2.3 [Other analyses]) at screening visit or Day -1.

8. The participant is a smoker or has used nicotine or nicotine-containing products (eg, snuff, nicotine pouch (eg, ZYN), nicotine patch, nicotine chewing gum, mock cigarettes, or vape cigarette alternatives, inhalers), marijuana, and cannabinoids within 1 year before the first dose of study drug.

9. The participant has donated blood in the past 90 days prior to screening or has poor peripheral venous access.

10. The participant has a diagnosis of chronic or acute liver disease, for example, auto-immune, alcoholic, or neoplastic liver disease.

11. The participant has positive serostatus for HIV, HCV, or HBV.

12. Male partners of females who are pregnant.

13. Female participant of childbearing potential who is pregnant, lactating, or planning to become pregnant within 90 days after the last dose of study drug.

14. The participant has received an investigational drug, biologic, or device within 3 months or 5 half-lives of the investigational drug (whichever is longer), before receiving study drug.

15. The participant has used any systemic medications, including vitamins and over-the-counter items, during the 14 days (or 5 times the elimination half-life of the medication, whichever is longer) before receiving study drug or will require their use during the study. Inducers and inhibitors of metabolic enzymes and/or transporters (in particular CYP3A inhibitors or inducers, P-gp, and BCRP), and herbal preparations, nutritional supplements (eg, St. John's Wort), or foods, including grapefruit juice, grapefruit/grapefruit-related citrus fruits (eg, Seville oranges, pomelos), which have been shown to produce metabolic enzyme or transporter induction or inhibition, are prohibited before 5 half-lives of the investigational drug prior to check-in (Day -1). Paracetamol ≤3000 mg/day will be allowed up to 2 consecutive days before dosing and during the outpatient phase of the study, as needed.

16. The participant has been on a diet incompatible with the on-study diet, in the opinion of the investigator or designee, within 30 days prior to the first dosing and throughout the study.

17. The participant is part of the clinical staff personnel or a family member of the clinical site staff.

4.3 OTHER SCREENING CONSIDERATIONS

For coronavirus disease of 2019 screening, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) testing will be conducted as per clinical research unit's policy at the time of conduction.

4.3.1 Lifestyle Restrictions

The following lifestyle restrictions will be followed by the participants throughout the study until EOS:

1. Participants will abstain from alcohol for 48 hours prior to study drug administration and until the last set of laboratory evaluations at EOS.

2. Participants will abstain from smoking and drug use for the duration of the study. List of drugs that will be screened at screening and check-in are provided in Section 6.2.3 (Other analyses).

3. Foods or herbal preparations, including grapefruit juice, grapefruit/grapefruit-related citrus fruits (eg, Seville oranges, pomelos), are prohibited for the duration of the study.

4.4 WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

4.4.1 Reasons for Withdrawal

Participants can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

The investigator may withdraw a participant from the study if the participant:

1. Is non-compliant with the protocol;
2. Experiences a SAE or intolerable AE(s) that in the investigator's opinion requires withdrawal from the study;
3. Has laboratory safety assessments that reveal clinically significant hematological or biochemical changes from baseline values;
4. Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria;
5. Requires a medication prohibited by the protocol; or
6. Requests an early discontinuation for any reason.

The investigator can also withdraw a participant upon the request of the sponsor, or if the sponsor terminates the study. Upon occurrence of an SAE or intolerable AE, the investigator will confer with the sponsor. If a participant is discontinued because of an AE, the event will be followed until it is resolved, stable, or judged by the investigator to be not clinically significant.

4.4.2 Handling of Withdrawals

Participants are free to withdraw from the study at any time upon request. Participant's participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

When a participant withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, any participant who withdraws from the study prematurely will undergo all EOS assessments. Any participant who fails to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. The status of participants who fail to complete final assessments will be documented in the eCRF.

4.4.3 Replacements

Any participant who is withdrawn or discontinued from the study may be replaced.

5. STUDY TREATMENTS

5.1 TREATMENTS ADMINISTERED

For Part A, each participant will be randomly assigned to 1 of 6 treatment sequences; the sequences will dictate the order in which each participant receives each of the planned treatments. Refer to Section 3 for a description of the treatment sequences.

For Part A, each participant will receive the following study treatments in a crossover design:

- Treatment 1: 900 mg plixorafenib (6 × 150 mg tablets) administered after overnight fast (fasted state).
- Treatment 2: 900 mg plixorafenib (6 × 150 mg tablets) + cobicistat (1 × 150 mg tablet) administered after overnight fast (fasted state).
- Treatment 3: 900 mg plixorafenib (6 × 150 mg tablets) + cobicistat (1 × 150 mg tablet) administered following a high fat, high caloric meal (fed state).

For Part B, each participant will be randomly assigned to 1 of 4 treatment sequences; the sequences will dictate the order in which each participant receives each of the planned treatments. Refer to Section 3 for a description of the treatment sequences.

For Part B, each participant will receive three of the following study treatments per randomization in a crossover design:

- Treatment A: 900 mg plixorafenib (6 × 150 mg tablets) administered after overnight fast (fasted state).
- Treatment B: 900 mg plixorafenib (6 × 150 mg tablets) administered following a high fat, high caloric meal (fed state-high fat meal).
- Treatment C: 900 mg plixorafenib (6 × 150 mg tablets) administered following a low-fat meal (fed state-low-fat meal).
- Treatment D: 900 mg plixorafenib (6 × 150 mg tablets) administered with 150 mg cobicistat (1 × 150 mg tablet) following a low-fat meal (fed state-low-fat meal).

There will be a washout of at least 7 days between dosing in each treatment period.

5.2 STUDY DRUGS

The study drugs that will be used are as follows:

Product	Supplied Formulation
Plixorafenib	150 mg tablet
Cobicistat	150 mg tablet

Plixorafenib is available as white to off-white oval tablet (uncoated or film-coated tablets) and contains the following inactive excipients: HPMCAS, sodium lauryl sulfate, microcrystalline cellulose, mannitol, croscarmellose sodium, silicon dioxide, and sodium stearyl fumarate. Film-coated tablets also contain titanium dioxide, polyvinyl alcohol, macrogol, and talc.

Further information on the study drug can be found in the Investigator's Brochure (Fore Biotherapeutics 2023).

Cobicistat (150 mg) tablet is commercially available and will be supplied or obtained by the clinical unit according to the study agreement and in accordance with local guidelines. Refer to the prescribing of cobicistat for more details on the formulation, preparation, storage conditions, the approved indications, known precautions, warnings, and adverse reactions. Cobicistat will be dispensed by the pharmacy staff at the clinical study site.

5.2.1 Study Drug Packaging and Storage

Fore Biotherapeutics will provide the investigator and clinical unit with adequate quantities of plixorafenib. Cobicistat will be provided by clinical unit. Detailed instructions for the preparation of study treatments will be provided in a separate pharmacy manual.

All study drugs must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. A temperature log to record compliance with storage conditions will be required to be maintained at the site.

Instructions regarding storage and handling of plixorafenib is provided in the pharmacy manual.

5.2.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. Accurate records will be kept regarding when and how much study drug is dispensed and used by each participant in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, and to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

5.3 METHOD OF ASSIGNING PARTICIPANTS TO TREATMENT GROUPS

The Contract Research Organization will generate the randomization schedule. Participants who meet all inclusion and none of the exclusion criteria will be randomly assigned to one of the 6 treatment sequences for Part A and one of the 4 treatment sequences for Part B as described in Section 3. Randomization numbers (in sequential order) will be assigned before the first dose of study drug is administered. There will be no stratification.

5.4 BLINDING

This is an open-label study.

5.5 TREATMENT COMPLIANCE

All doses of the study drug will be administered in the clinical unit under direct observation of clinic personnel and recorded in the eCRF. Clinic personnel will confirm that the participant has received the entire dose of study drug.

The date and time of study drug dosing will be recorded on the appropriate page of the eCRF. If a participant is not administered study drug, the reason for the missed dose will be recorded.

5.5.1 Prior and Concomitant Medications

Prohibited and/or restricted prior and concomitant medications and therapies are provided in Sections 4.2 and 5.5.1.2.1. Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary.

5.5.1.1 Prior Medications

Information regarding prior medications taken by the participant within the 30 days before signing the ICF will be recorded in the participant's eCRF.

5.5.1.2 Concomitant Medications

During the study, any concomitant medication deemed necessary for the welfare of the participant may be given at the discretion of the investigator. If a concomitant medication is taken, except for those specified in the protocol, a joint decision will be made by the investigator and the sponsor to continue or discontinue the participant based on the time the medication was administered, its pharmacology and PK, the potential for drug interactions, and whether the use of the medication will compromise the safety of the participant or the interpretation of the data. The investigator is responsible for ensuring that details regarding the medication are adequately recorded in the eCRF.

5.5.1.2.1 Prohibited Medications

Agents that are known strong inducers or inhibitors of CYP3A4 are prohibited throughout the study. Herbal medications including St. John's Wort, are prohibited, throughout the study. Agents that are contraindicated with cobicistat are prohibited throughout the study.

6. STUDY PROCEDURES

Before performing any study procedures, all potential participants will sign an ICF as outlined in Section 9.2.2.3. Participants will undergo study procedures at the time points specified in the SOE (Section 3.3).

The total amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

6.1 PHARMACOKINETIC AND PHARMACOGENOMICS ASSESSMENTS AND ENDPOINTS

Following administration of the study treatments, participants will have serial blood drawn (Part A and Part B) and urine (for Part A only) samples collected for determination of blood and urine concentration of plixorafenib.

Blood PK sample collection timepoints are provided in Table 6-1.

Table 6-1 Blood PK Sampling Timepoints

Study Days Timepoints	D1, D8, D15 (Dosing)	D2, D9, D16	D3, D10, D17	D4, D11, D18	D5, D12, D19
0 hour (0800)*	✓ (Predose)**	✓ (24 h)	✓ (48 h)	✓ (72 h)	✓ (96 h)
0.5 hour (0830)	✓				
1 hour (0900)	✓				
2 hour (1000)	✓				
3 hour (1100)	✓				
4 hour (1200)	✓				
6 hour (1400)	✓				
8 hour (1600)	✓	✓ (32 h)			
10 hour (1800)	✓				
12 hour (2000)	✓				

D, day; h, hours

*Nominal clock time.

**Predose sample will be collected within 15 minutes prior to the dosing. 0 hour means dosing of study drug.

For Part A only: Prior to the predose sample, each participant will be instructed as to urine collection methods. Urine samples for the determination of plixorafenib concentrations and its metabolites will be collected at selected time intervals, as specified in the table below. All participants will be asked to void their bladder within 45 minutes prior to dosing. After administration of plixorafenib, all urine will be collected completely per each collection interval. Urine portions will be pooled per participant within this collection interval. Just prior to the end of the sampling interval, participants will be encouraged to void their bladder again to complete the collection. The start and end times of the urine collection will be recorded. Three aliquot (5 mL each) will be obtained from each pooled urine sample: 1 for the quantification of plixorafenib, 1 for the metabolite analysis, and 1 as a back-up. Instructions for sample preparation and storage can be found in the study lab manual.

Urine samples for the quantitation of plixorafenib, collection timepoints are in Table 6-2.

Table 6-2 Urine Sample Collection Timepoints

Study Days Timepoints	D1, D8, D15 (Dosing Day)	D2, D9, D16
Predose*	✓	

Study Days Timepoints	D1, D8, D15 (Dosing Day)	D2, D9, D16
0-4 hours	✓	
4-8 hours	✓	
8-12 hours	✓	
12-24 hours		✓
24-48 hours		✓

D, days.
*45 minutes prior to dosing.

The following PK parameters will be calculated using model-independent approaches (NCA) from plixorafenib individual plasma concentrations, whenever practical.

Plasma Parameters (Part A and B)

- Area under the plasma concentration versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}).
- AUC from time 0 extrapolated to infinity (AUC_{0-inf}).
- Maximum observed plasma concentration (C_{max}).
- Time to maximum observed plasma concentration (T_{max}).
- Terminal elimination rate constant (K_{el}).
- Terminal phase half-life ($t_{1/2}$).
- Apparent oral clearance (CL/F).
- Apparent volume of distribution (V_d/F).
- Terminal rate constant calculated from the terminal slope of the log-linear regression of concentration with time (λ_z).
- Calculated lag time: time taken for the drug to appear in the systemic circulation following administration, when applicable (T_{lag}).

Urine Parameters (Part A Only)

- Cumulative amount of plixorafenib excreted in urine, calculated as the sum of the product of urine concentration and urine volume (A_e)
- Percent of dose excreted in urine in 48 hours calculated as $100*A_e$/Dose

Blood and urine samples may be used to evaluate the metabolic profile of plixorafenib and the results will be described separately.

Blood and/or plasma samples may be used to measure endogenous biomarkers, such as coproporphyrin I, to assess possible transporters inhibition.

6.1.1 Pharmacokinetic Sample Collection

Details for the collection, processing, storage, and shipping of PK samples will be provided to the clinical unit separately.

6.1.2 Pharmacokinetic Sample Analysis

Plasma samples for the quantitation of plixorafenib will be analyzed using a validated liquid chromatography coupled with tandem mass spectrometry assay (LC/MS/MS method) for plixorafenib in human plasma. Assay results and validation details will be provided in a separate bioanalytical report. A qualified assay will be used to quantitate plixorafenib urine concentrations. An exploratory assay will be used for metabolite identification in plasma and urine.

6.1.3 Pharmacogenomic Sample Analysis

A blood sample for pharmacogenomic evaluation will be collected at screening. Possible effect of pharmacogenomic variations on the PK of plixorafenib and/or the effect of cobicistat, including but not limited to polymorphisms in P-gp, BCRP, and UGT, will be examined, if feasible.

6.2 SAFETY ASSESSMENTS AND ENDPOINTS

Safety will be assessed by the following: monitoring and recording of AEs, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECG results, and physical examination findings.

For all safety assessments, the investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance or may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented and an AE reported on the AE page of the participant's eCRF. The investigator will monitor the participant until the result has reached the reference range or the result at screening, or until the investigator determines that follow-up is no longer medically necessary.

6.2.1 Sponsor Communication

The sponsor Medical Monitor will be contacted as quickly as possible for Grade 2 or above changes in blood AST, ALT, GGT, bilirubin (total or fractionated), or creatinine, or ≥ Grade 3 laboratory abnormalities or adverse events. Communication with the sponsor Medical Monitor should not delay immediate management of the participant.

6.2.2 Adverse Events

Adverse events will be assessed from the time the participant signs the ICF until EOS and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the sponsor, regardless of their relationship to study drug or clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

6.2.2.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Participants will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. TEAE will be assessed from first dose of study drug until EOS and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, “reasonable possibility” means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or if it occurs with specificity or severity that has not been previously observed with the study drug being tested; or, if an investigator brochure is not required or available, the AE or suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

An AE is considered an SAE/suspected unexpected serious adverse reaction if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE

- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the investigator or sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE or suspected adverse reaction that might have caused death if it had been more severe.

6.2.2.2 Eliciting and Documenting Adverse Events

Participants will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to participant's observations, AEs will be documented from any data collected on the AE page of the eCRF (eg, laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to participant safety.

6.2.2.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dosage, investigator-specified assessment of severity, seriousness, and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. The Medical Dictionary of Regulatory Activities will be used to code all AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that is considered serious by the investigator or which meets SAE criteria (Section 6.2.2.1) must be reported to the sponsor immediately (after the investigator has confirmed the occurrence of the SAE). The investigator will assess whether there is a reasonable possibility that the study drug caused the SAE. The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in US Title 21 CFR Parts 312 and 320. The investigator is responsible for notifying the IRB directly.

For this study, the following contact information will be used for SAE reporting:

ICON Drug Safety
ICON-Safety-CentralReceipt@iconplc.com
Fax: +44 (0) 208 100 5005

6.2.2.4 Assessment of Severity

Seriousness (Section 6.2.2.1) and severity of an event are not synonymous. The severity (or intensity) of an AE refers to the extent to which it affects the participant's daily activities and will be classified as mild, moderate, or severe using the following criteria:

- Mild: These events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate: These events result in a low level of inconvenience or require minor therapeutic measures. Moderate events may cause some interference with normal functioning.
- Severe: These events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow the duration of the event at each level of intensity to be assessed. An AE characterized as intermittent does not require documentation of the onset and duration of each episode.

The Common Toxicity Criteria for Adverse Events (CTCAE) V5.0 grading criteria will also be used for assessment of severity of AEs.

6.2.2.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be classified as follows:

- Not related: The adverse event is considered unrelated to the study drug.
    - Another cause of the event is most plausible, or

- Clinically plausible temporal sequence is inconsistent with the onset of the event and the study treatment administration
- A causal relationship is considered biologically implausible

- Possibly related: Based on evidence suggesting a causal relationship between the study drug and the AE, there is a reasonable possibility that the drug caused the event. The event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

- Probably related: A reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, association of the event with the study drug seems likely.

6.2.2.6 Adverse Event of Special Interest

The following are AESIs for this study:

- Grade ≥2 increased bilirubin
- Grade ≥2 increased ALT
- Grade ≥2 increased AST

The sponsor Medical Monitor will be notified promptly of AESIs. AESIs will be reported using the same process as for AEs.

6.2.2.7 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

6.2.3 Clinical Laboratory Testing

Clinical laboratory testing will occur at screening, check-in, predose within 2 hours on each dosing day (Days 1, 8, and 15) (for Part B only), 3 days from dosing (Day 4, 11, 18), and at EOS. Clinical laboratory tests will be performed by the PPD Central Laboratory. Blood and urine samples will be collected under fasting conditions and will be prepared using standard procedures. If any concerning trends are seen during study, investigator can order additional testing for safety on PRN basis.

Repeat clinical laboratory tests may be performed at the discretion of the investigator, if necessary, to evaluate inclusion and exclusion criteria or clinical laboratory abnormalities. The clinical laboratory that will perform the tests will provide the reference ranges for all clinical laboratory parameters. Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter.

The following clinical laboratory assessments will be performed:

Hematology	Absolute neutrophil count and differential, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, leukocytes-absolute counts and percentages (basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume, platelet count, red blood cell count, and red cell distribution width
Serum Chemistry	Alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin (total + indirect and direct fractions), blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, uric acid, and creatine kinase
Urinalysis	Appearance, bilirubin, color, glucose, ketones, leukocytes, reflex microscopy (performed if dipstick is positive for protein or the blood value is 1+ or greater; and includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, turbidity, and urobilinogen
Serology	Hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antibody types 1 and 2 (screening only)
Other analyses	All participants: Urine drug screen (alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, cotinine, methamphetamines, methylenedioxymethamphetamine, and opiates [including heroin, codeine, and oxycodone]) Female participants: Follicle-stimulating hormone, urine pregnancy test/ serum pregnancy test (human chorionic gonadotropin)

6.2.4 Vital Sign Measurements

Vital signs will be measured at screening and check-in; within 60 to 90 minutes prior to plixorafenib dosing in each period; on each study day; and at EOS after the participant has been in the seated position for at least 5 minutes.

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

6.2.5 Electrocardiograms

Single 12-lead ECG recordings will be made at screening, each dosing day (Days 1, 8, and 15)-predose within 2 hours, and at EOS after the participant has been in the supine position for at least 5 minutes. A single repeat measurement is permitted at screening for eligibility determination.

ECG assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST-segment, T-Wave, and U-Wave abnormalities. In addition, measurements of the

following intervals will be measured and reported: RR interval, PR interval, QRS width, QT interval, and QT interval corrected for heart rate using Fridericia's formula.

6.2.6 Physical Examinations

Physical examinations will be performed at screening, check-in, at each dosing day (Days 1, 8, 15), and at EOS (Day 19).

A full physical examination will be performed at screening and check-in. A symptom-driven physical examination may be performed at other times, at the investigator's or designee's discretion.

A full physical examination will include, at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. A brief physical examination will include, at minimum, assessment of skin, lungs, cardiovascular system, and abdomen (liver and spleen). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

7. STATISTICAL ANALYSIS PLANS

7.1 SAMPLE SIZE CALCULATIONS

The number of participants is based on clinical and practical considerations and not on a formal statistical power calculation. The total sample size of 12 participants in Part A and 16 participants in Part B is considered sufficient for the objectives of the study.

7.2 ANALYSIS SETS

The analysis populations are as follows:

- The PK population will include participants who receive at least 1 dose of plixorafenib with or without cobicistat and have sufficient concentration data to support accurate estimation of at least 1 PK parameter. Participants who experience vomiting within 2 times the median T_{max} after study drug dosing will be excluded from the PK analysis.

- The safety population will include all participants who receive at least 1 dose plixorafenib with or without cobicistat.

7.3 STATISTICAL ANALYSIS

Details of all statistical analyses will be described in a statistical analysis plan. All data collected will be presented in data listings. Data from participants excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, SD, minimum, and maximum).

Baseline demographic and background variables will be summarized overall for all participants. The number of participants who enroll in the study and the number and percentage of participants who complete the study will be presented. Frequency and percentage of participants who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

7.3.1 Pharmacokinetic Analyses

Individual plasma concentration and time deviation data will be presented in a data listing. Plasma concentration data will be summarized by time point for each treatment (plixorafenib alone in fasted state, plixorafenib + cobicistat in fasted state or plixorafenib + cobicistat in fed state) using the following descriptive statistics: number of participants, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. Individual and mean plasma concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales.

The PK parameters of plixorafenib will be determined using noncompartmental methods based on the actual sampling times. All parameters will be calculated using Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.3 or higher. The individual PK parameters will be presented in data listings and summarized by treatment using the following descriptive statistics: number of participants, mean, SD, CV, median, minimum, and maximum. Geometric means will be included for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}.

If warranted, a linear mixed model with treatment as a fixed effect and participant as a random effect will be performed on the natural log-transformed values of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} to assess the effect of cobicistat and/or food on the PK of plixorafenib. The geometric least squares means and corresponding 90% CIs will be computed for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} of plixorafenib administered alone (Reference Treatment) versus plixorafenib with cobicistat and/or food (Test Treatments) by taking the antilog of the least squares means from the linear mixed-effect model on the natural logarithms of the corresponding PK parameters. A 90% CI for the ratio will be constructed as the antilog of the confidence limits of the mean difference.

It will be concluded that there is no relevant interaction of cobicistat or food on plixorafenib if the 90% CIs for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} ratios of the Reference Treatment to the Test Treatments are completely contained within the (80%, 125%) interval.

The statistical analysis plan will include a more detailed description of these analyses.

7.3.2 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of MedDRA. All AE data will be presented in a data listing. TEAEs will be summarized by treatment and overall, as well as by severity, seriousness, and relationship to study drug. Serious

AEs and AEs leading to discontinuation of study drug will also be presented in the data listings and summarized by treatment and overall.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of participants, mean, SD, median, minimum, and maximum). Physical examination findings will be presented in a data listing.

For safety analysis, unless stated otherwise, baseline will be defined as the last nonmissing assessment (including repeat and unscheduled assessments) predose for each period. An overall baseline for by-sequence analysis will be defined as the last value prior to Day 1 dose.

7.3.3 Other Analyses

Evaluation of the metabolic profile of plixorafenib in plasma (Parts A and B) and urine (Part A only) will be conducted and the results will be reported separately.

For Part A and Part B, possible effect of pharmacogenomic variations on the PK of plixorafenib and/or the effect of cobicistat, including, but not limited to, polymorphisms in P-gp, BCRP, and UGT, will be examined, if feasible.

7.4 HANDLING OF MISSING DATA

Missing data will not be interpolated or extrapolated.

7.5 INTERIM ANALYSES

No formal interim analyses will be performed in this study.

8. REFERENCE LIST

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9. APPENDICES

9.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
λ_z	terminal rate constant calculated from the terminal slope of the log-linear regression of concentration with time
A_e	cumulative amount of plixorafenib excreted in urine
ADR	adverse drug interactions
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-inf}}$	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
$AUC_{0\text{-t}}$	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
BCRP	Breast cancer resistance protein
β-hCG	beta-subunit human gonadotropin
BMI	body mass index
BSEP	bile salt export pump
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent oral clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CV	coefficient of variation
CYP	cytochrome P450
DLT	dose limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOS	end of study
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GLP	good laboratory practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HME	hot-melt extrusion
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form

Abbreviation	Term
ICH	International Council for Harmonisation
IRB	institutional review board
LCH	Langerhans cell histiocytosis
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion transporter
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK/ERK kinase
MRP	multidrug resistance associated protein
NCA	Noncompartmental analysis
NOAEL	no-observed-adverse-effect levels
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PK	pharmacokinetic(s)
P-gp	P-glycoprotein
PRN	as needed
QTcF	QT correction (Fridericia)
RAF	rapidly accelerated fibrosarcoma
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SDD	spray-dried dispersion
SOE	schedule of events
$t_{1/2}$	terminal phase half-life
TEAE	treatment-emergent adverse events
T_{max}	time to maximum observed plasma concentration
UGT	uridine diphosphate (UDP)-glucuronosyltransferases
ULN	upper limit of normal
V_d/F	apparent volume of distribution

9.2 APPENDIX 2: STUDY GOVERNANCE

9.2.1 Data Quality Assurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current ICH guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice, the protocol, and standard operating procedures. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability.

Important protocol deviations, should they occur during the study, will be presented in Section 10.2 of the clinical study report.

9.2.2 Investigator Obligations

The following administrative items are meant to guide the investigator in the conduct of the study and may be participant to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.2.2.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2.2.2 Institutional Review

Federal regulations and ICH guidelines require that approval be obtained from an IRB before participation of human participants in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study participants, and any other written information regarding this study that is to be provided to the participants must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH

harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

9.2.2.3 Participant Consent

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each participant before he or she enters the study or before performing any unusual or nonroutine procedure that involves risk to the participant. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating participants must sign the revised form.

Before recruitment and enrollment, each prospective participant will be given a full explanation of the study and will be allowed to read the approved ICF. Once the investigator is assured that the participant understands the implications of participating in the study, the participant will be asked to give his or her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the participant.

9.2.2.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate.

9.2.2.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the disease under study.

9.2.2.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and US Title 21 of the CFR by providing essential documents, including but not limited to, the following:

- IRB approval
- An original investigator-signed investigator agreement page of the protocol,
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. Curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information for the principal investigator and each subinvestigator listed on Form FDA 1572 to allow the sponsor to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the participant
- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with US Title 42 CFR Part 493

9.2.2.7 Study Conduct

The investigator agrees to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6(R2): Good Clinical Practice; the protocol; and all national, state, and local laws or regulations.

9.2.2.8 Case Report Forms and Source Documents

Site personnel will maintain source documentation, enter participant data into the eCRF as accurately as possible, and will rapidly respond to any reported discrepancies.

Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new participants, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

9.2.2.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.2.2.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

9.2.2.11 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authorities with any reports required.

9.2.2.12 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. The sponsor is responsible for informing the investigator/institution when these documents no longer need to be retained.

9.2.2.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without their prior authorization, but data and any publication thereof will not be unduly withheld.

9.2.3 Study Management

9.2.3.1 Monitoring

9.2.3.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

9.2.3.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, the FDA, or other regulatory agencies access to all study records.

The investigator should promptly notify the sponsor and study site(s) of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

9.2.3.2 Management of Protocol Amendments and Deviations

9.2.3.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the participant, must be reviewed and approved by the sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before participants are enrolled into an amended protocol.

9.2.3.2.2 Protocol Deviations

The investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments

should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a participant being discontinued from the study, or significantly affects the participant's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations, if appropriate, in a timely manner.

9.2.3.3 Study Termination

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

9.2.3.4 Final Report

Regardless of whether the study is completed or prematurely terminated, the sponsor will ensure that clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

Upon completion of the clinical study report, the investigator(s) will be provided with the final approved clinical study report, as appropriate.