

Fore Biotherapeutics

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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Final Statistical Analysis Plan

Version 2.0

Prepared by:

PPD
3900 Paramount Parkway
Morrisville, NC 27560 USA

Confidential

Table of Contents

LIST OF ABBREVIATIONS	3
1. INTRODUCTION	5
2. OBJECTIVES AND ENDPOINTS	6
2.1 PRIMARY OBJECTIVES	6
2.2 SECONDARY OBJECTIVES	7
2.3 EXPLORATORY OBJECTIVES	8
3. STUDY DESIGN.....	8
3.1. PART A.....	8
3.2. PART B.....	10
4. GENERAL STATISTICAL CONSIDERATIONS	11
4.1. SAMPLE SIZE	13
4.2. RANDOMIZATION AND BLINDING	13
4.3. ANALYSIS SETS.....	14
5. PARTICIPANT DISPOSITION	14
5.1. DISPOSITION	14
5.2. PROTOCOL DEVIATIONS	16
5.3. INCLUSION AND EXCLUSION CRITERIA.....	16
6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS	17
6.1. DEMOGRAPHICS	17
6.2. MEDICAL HISTORY	17
7. TREATMENTS AND MEDICATIONS.....	17
7.1. PRIOR AND CONCOMITANT MEDICATIONS	17
7.2. STUDY TREATMENT	18
8. SAFETY ANALYSIS	18
8.1. ADVERSE EVENTS	18
8.2. CLINICAL LABORATORY EVALUATIONS.....	20
8.3. VITAL SIGN MEASUREMENTS.....	22
8.4. PHYSICAL MEASUREMENTS.....	22
8.5. PHYSICAL EXAMINATION	22
8.6. ELECTROCARDIOGRAMS.....	23
9. OTHER ANALYSIS.....	23
10. INTERIM ANALYSIS	23
11. CHANGES IN THE PLANNED ANALYSIS	24
12. REFERENCES.....	25
13. SCHEDULE OF ASSESSMENTS	26

List of Abbreviations

AE	adverse event
A _e	cumulative amount of drug excreted in urine
A _{e,48}	cumulative amount of drug excreted in urine from 0 to 48 hours
AESI	adverse event of special interest
AUC	area under the curve
AUC _{0-∞}	area under the curve from time 0 extrapolated to infinity
AUC _{0-t}	area under the curve from time 0 to the last measurable observed concentration
BCRP	breast cancer resistance protein
BID	twice daily dosing
BMI	body mass index
CL/F	apparent oral clearance
C _{max}	maximum observed plasma concentration
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
FDA	US food and drug administration
ICH	International Council for Harmonization
INDs	investigational new drug applications
K _{el}	terminal elimination rate constant
MAPK	mitogen-activated protein kinases
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug applications
P-gp	P-glycoprotein
PK	pharmacokinetic
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
t _{1/2}	terminal phase half-life
TEAE	treatment-emergent adverse event
T _{lag}	calculated lag time

TLFs	tables, listings, and figures
T _{max}	time of maximum observed concentration
UGT	uridine diphosphate (UDP)-glucuronosyltransferases
V _d /F	apparent volume of distribution
λ _z	terminal rate constant

1. Introduction

The purpose of this statistical analysis plan (SAP) is to define the planned statistical analysis of the study data consistent with the study objectives, except PK analysis which is detailed in a separate PK analysis plan. This SAP is written based on amendment 1 of protocol F8394-101, dated 3rd October 2024.

Plixorafenib is a first-in-class next-generation orally available selective potent v-RAF murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor that blocks mutant BRAF cells without activating the mitogen-activated protein kinases (MAPK) pathway in cells containing an upstream activation event. Plixorafenib has nonclinical and clinical activity against both monomeric V600 mutations and dimeric non-V600 BRAF alterations, including BRAF fusions and deletion mutations.

As of 29 January 2024, a total of 174 participants have been exposed to study drug in clinical trials.

In the completed 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 area under the curve (AUC) from 0 to the last measurable concentration (AUC_{0-t}) and from 0 extrapolated to infinity ($AUC_{0-\infty}$) increased 2.6-fold (300 mg level) and 3.8-fold (900 mg level), and the mean maximum observed plasma concentration (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.

In the ongoing study PLX120-03, preliminary pharmacokinetic (PK) data from 84 subjects showed that when plixorafenib was administered alone, a modest increase in exposure was observed between the 450 mg twice daily dosing (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.

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.

Cobicistat is a PK booster that may be 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.

This study will assess the effect of food on the single-dose PK of plixorafenib administered with cobicistat in accordance with the US food and drug administration (FDA) guidance for industry on assessing the effects of food on drugs in investigational new drug applications (INDs) and new drug applications (NDAs) [DHHS 2002].

This study will also assess the effects of cobicistat administration on the single-dose PK of plixorafenib.

This study is designed in two parts, Part A and Part B. Part B objectives and rationale were determined after the review of Part A results. 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 $\geq 50\%$ from fat) on the exposure of plixorafenib will be examined in Part B of this study, compared to the fasted state.

This SAP describes the analysis for Part A and Part B.

2. Objectives and Endpoints

2.1 Primary Objectives

Primary objectives	Endpoint Description
Part A	
<ul style="list-style-type: none">To examine the effect of food on the single dose PK of plixorafenib administered with cobicistat.	<ul style="list-style-type: none">Plasma PK parameters of plixorafenib (AUC_{0-t}, $AUC_{0-\infty}$, C_{\max},

	T_{\max} , K_{el} , $t_{1/2}$, CL/F , V_d/F , λ_z , and T_{lag}).
<ul style="list-style-type: none"> To examine the effect of cobicistat administration on the single dose PK of plixorafenib. 	<ul style="list-style-type: none"> Urine PK parameters of plixorafenib (A_e, and $100 \cdot A_e / \text{Dose}$).
<ul style="list-style-type: none"> To determine the safety of plixorafenib administered alone and with cobicistat in a single dose regimen in healthy participants. 	<ul style="list-style-type: none"> Adverse Events (AEs), clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12 lead Electrocardiogram (ECG) results, and physical examination findings.
Part B	
<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Plasma PK parameters of plixorafenib (AUC_{0-t}, $AUC_{0-\infty}$, C_{\max}, T_{\max}, K_{el}, $t_{1/2}$, CL/F, V_d/F, λ_z, and T_{lag}).
<ul style="list-style-type: none"> To determine the safety of plixorafenib administered alone or with cobicistat (low-fat meal only) in a single dose regimen. 	<ul style="list-style-type: none"> Adverse Events (AEs), clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12 lead Electrocardiogram (ECG) results, and physical examination findings.

2.2 Secondary Objectives

Secondary objectives	Endpoint Description
Part A	
<ul style="list-style-type: none"> To characterize metabolites of plixorafenib in plasma and urine. 	<ul style="list-style-type: none"> Evaluation of the metabolic profile of plixorafenib in plasma and urine

<ul style="list-style-type: none">To characterize the urinary excretion of plixorafenib.	<ul style="list-style-type: none">Urine PK parameters of plixorafenib (Ae, and 100*Ae/Dose).
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2.3 Exploratory Objectives

Part A

- To examine the possible effect of pharmacogenomic variations on the PK of plixorafenib and/or the effect of cobicistat, including polymorphisms in P-glycoprotein (P-gp), breast cancer resistant protein (BCRP), and uridine diphosphate-glucuronosyltransferases (UGT).

Part B

- 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 plixorafenib on endogenous biomarkers such as coproporphyrin may be evaluated.

3. Study Design

Schedules of assessments can be found in [Section 13](#).

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.

Part A will consist of a screening period, one check-in, three treatment periods (with a 7-day washout between dosing in each period), and an end of study (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.

Participants will be randomized to 1 of 6 treatment sequences at a 1:1:1:1:1:1 ratio.

Table 3-2 Treatment Sequences for Part A

Treatment Sequence Number	Treatment Sequence*	Treatment Period 1	Treatment Period 2	Treatment Period 3
1	1:2:3	900 mg plixorafenib (Fasted)	900 mg plixorafenib + 150 mg cobicistat (Fasted)	900 mg plixorafenib + 150 mg cobicistat (Fed)
2	2:3:1	900 mg plixorafenib + 150 mg cobicistat (Fasted)	900 mg plixorafenib + 150 mg cobicistat (Fed)	900 mg plixorafenib (Fasted)
3	3:2:1	900 mg plixorafenib + 150 mg cobicistat (Fed)	900 mg plixorafenib + 150 mg cobicistat (Fasted)	900 mg plixorafenib (Fasted)
4	2:1:3	900 mg plixorafenib + 150 mg cobicistat (Fasted)	900 mg plixorafenib (Fasted)	900 mg plixorafenib + 150 mg cobicistat (Fed)
5	3:1:2	900 mg plixorafenib + 150 mg cobicistat (Fed)	900 mg plixorafenib (Fasted)	900 mg plixorafenib + 150 mg cobicistat (Fasted)
6	1:3:2	900 mg plixorafenib (Fasted)	900 mg plixorafenib + 150 mg cobicistat (Fed)	900 mg plixorafenib + 150 mg cobicistat (Fasted)

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

All participants will fast overnight for at least 10 hours prior to treatment. When receiving fasted treatments [900 mg plixorafenib, or 900 mg plixorafenib + 150 mg cobicistat (Fasted)], participants will continue to fast for at least 4 hours after dosing. When receiving the 'fed' treatment [900 mg plixorafenib + 150 mg cobicistat (Fed)], participants will receive a high caloric meal prior to dosing. Participants must consume the entire meal within 30 min of serving; the percentage of meal consumed will be documented. Dosing must occur 30 min (\pm 5 min) after the start of the meal. Participants receiving 'fed' treatment will receive their next meal no less than 4 hours after dosing.

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. 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.

Part B 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-:

Table 3-3 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.

Participants will be randomized to 1 of 4 treatment sequences at a 1:1:1:1 ratio.

Table 3-4 Treatment Sequences for Part B

Treatment Sequence Number	Treatment Sequence*	Treatment Period 1	Treatment Period 2	Treatment Period 3
1	A:C:D	900 mg plixorafenib (Fasted)	900 mg plixorafenib (Low Fat Meal)	900 mg plixorafenib + 150 mg cobicistat (Low Fat Meal)
2	B:D:A	900 mg plixorafenib (High Fat Meal)	900 mg plixorafenib + 150 mg cobicistat (Low Fat Meal)	900 mg plixorafenib (Fasted)
3	D:B:C	900 mg plixorafenib + 150 mg cobicistat (Low Fat Meal)	900 mg plixorafenib (High Fat Meal)	900 mg plixorafenib (Low Fat Meal)
4	C:A:B	900 mg plixorafenib (Low Fat Meal)	900 mg plixorafenib (Fasted)	900 mg plixorafenib (High Fat Meal)

* Treatment A: 900 mg plixorafenib administered after overnight fast (fasted state), Treatment B: 900 mg plixorafenib administered following a high-fat high caloric meal (fed state-high fat meal), Treatment C: 900 mg plixorafenib administered following a low-fat meal (fed state-low-fat meal), 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 fasted treatment (900 mg plixorafenib administered after overnight fast) will continue to fast for at least 4 hours after dosing.
- Participants receiving a ‘high fat’ treatment (900 mg plixorafenib administered following a high-fat high caloric meal) will receive a high fat ($\geq 50\%$ 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 a ‘low fat’ treatment (either 900 mg plixorafenib administered following a low-fat meal, or, 900 mg plixorafenib administered with 150 mg cobicistat following a low-fat meal) 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.

Participants on ‘high fat’ or ‘low fat’ treatment must consume the entire meal within 30 min of serving; the percentage of meal consumed will be documented. Dosing must occur 30 min (± 5 min) after the start of the meal. Participants receiving ‘high fat’ or ‘low fat’ treatment will receive their next meal no less than 4 hours after dosing.

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. 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.

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Descriptive statistics for continuous variables will include number of participants, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. For categorical variables, frequencies and percentages will be presented.

All tables, listings, and figures (TLFs) will be presented by part, and where applicable either; overall, or by treatment, or by treatment and overall, or by treatment sequence.

When presented by treatment, the treatments below will be used for presentations:

- Part A:
 - 900 mg plixorafenib (Fasted)
 - 900 mg plixorafenib + 150 mg cobicistat (Fasted)
 - 900 mg plixorafenib + 150 mg cobicistat (Fed)
- Part B:
 - 900 mg plixorafenib (Fasted)
 - 900 mg plixorafenib (High Fat)
 - 900 mg plixorafenib (Low Fat)
 - 900 mg plixorafenib + 150 mg cobicistat (Low Fat)

In addition to analysis by Part A and Part B, pooled analysis by treatment may be conducted as exploratory analysis.

All data listings will be sorted by participant number and collection date where applicable.

No algorithm for imputation of missing data will be employed.

For Part A and B, study days are calculated with respect to the first dose date of any study drug as below:

- If the assessment/observation date is on or after the first dose date of any study drug, then
Study Day = Assessment/Observation Date – First Dose Date of any study drug + 1;
- Otherwise,
Study Day = Assessment/Observation Date – First Dose Date of any study drug.

Unless stated otherwise, for safety analysis in Part A and B, baseline will be defined as the last non-missing assessment (including repeat and unscheduled assessments) pre-dose for each period. This may include a post-dose assessment for the previous period (for example, Day 4 assessment of Treatment Period 1 may be considered a baseline assessment for Treatment Period

2 when a subject has no pre-dose assessments for period 2). Unless stated otherwise, baseline for analysis by sequence is defined as the last assessed value prior to dosing on Day 1 of Period 1.

For summaries of safety assessments, if there are repeated measurements at a time point, the first non-missing assessment at that time point will be used in the summary tables.

For summaries of safety assessments, the maximum and minimum postbaseline result (where applicable), will be selected as the highest and lowest result (respectively) collected after baseline, including repeated and unscheduled assessments.

Unscheduled results will not be included in the summary tables by visit, except for determining Baseline or postbaseline minimum and maximum, but will be presented in data listings.

For Part A and B, to compare the post baseline results of the same treatment across different treatment periods, summaries by treatment and timepoint will standardize the visits as follows:

Analysis Visit	Recorded Visit
Baseline	Baseline result as defined above
Day 2	Day 2, Day 9, or Day 16
Day 3	Day 3, Day 10, or Day 17
Day 4	Day 4, Day 11, or Day 18
Day 5	Day 5, Day 12, or Day 19/EOS

The methodology and data handling specifications for PK data will be described in a separate analysis document created by the sponsor, *Fore Biotherapeutics*, or their designee. Any PK data needed for analysis, such as for derivations of analysis sets (see [Section 4.3](#)), will be received from the sponsor, *Fore Biotherapeutics*, or their designee.

4.1. 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.

4.2. Randomization and Blinding

This is an open-label study, as such, no considerations for blinding are required.

In Part A, participants who meet all inclusion and none of the exclusion criteria will be randomly assigned to one of the 6 treatment sequences as described in [Section 3.1](#). Randomization

numbers (in sequential order) will be assigned before the first dose of study drug is administered. There will be no stratification.

In Part B, participants who meet all inclusion and none of the exclusion criteria will be randomly assigned to one of the 4 treatment sequences as described in [Section 3.2](#). Randomization numbers (in sequential order) will be assigned before the first dose of study drug is administered. There will be no stratification.

4.3. Analysis Sets

Part A and Part B

The safety set will include all participants who received at least 1 dose of plixorafenib.

The PK population will include participants who receive at least 1 dose of plixorafenib 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.

For Part A, all enrolled participants may be used for analysis. This set will include all participants who, according to the study investigator on the electronic case report form (eCRF), had met all eligibility criteria and were ready for randomization, regardless of whether they were then randomized or not.

5. Participant Disposition

5.1. Disposition

For Part A, the following will be summarized for all enrolled participants:

- The number of participants randomized.

For Part A, the following will be summarized for the participants in the safety set, by treatment sequence and overall:

- The number of participants who received plixorafenib alone in a fasted state.
- The number of participants who received plixorafenib and cobicistat in a fasted state.
- The number of participants who received plixorafenib and cobicistat in a fed state.
- The number of participants who were treated in treatment period 1.

- The number of participants who were treated in treatment period 2.
- The number of participants who were treated in treatment period 3.
- The number of participants who completed treatment period 1.
- The number of participants who did not complete treatment period 1 (both overall and according to reasons for discontinuation from the treatment period 1).
- The number of participants who completed treatment period 2.
- The number of participants who did not complete treatment period 2 (both overall and according to reasons for discontinuation from the treatment period 2).
- The number of participants who completed treatment period 3.
- The number of participants who did not complete treatment period 3 (both overall and according to reasons for discontinuation from the treatment period 3).
- The number of participants who completed the study.
- The number of participants who did not complete the study (both overall and according to reasons for discontinuation from the study).
- The number of participants in the safety and PK analysis sets.

For Part B, the following will be summarized for the participants in the safety set, by treatment sequence and overall:

- The number of participants who received plixorafenib alone in a fasted state.
- The number of participants who received plixorafenib alone after a low-fat meal.
- The number of participants who received plixorafenib alone after a high-fat meal.
- The number of participants who received plixorafenib and cobicistat after a low-fat meal.
- The number of participants who were treated in treatment period 1.
- The number of participants who were treated in treatment period 2.
- The number of participants who were treated in treatment period 3.

- The number of participants who completed treatment period 1.
- The number of participants who did not complete treatment period 1 (both overall and according to reasons for discontinuation from the treatment period 1).
- The number of participants who completed treatment period 2.
- The number of participants who did not complete treatment period 2 (both overall and according to reasons for discontinuation from the treatment period 2).
- The number of participants who completed treatment period 3.
- The number of participants who did not complete treatment period 3 (both overall and according to reasons for discontinuation from the treatment period 3).
- The number of participants who completed the study.
- The number of participants who did not complete the study (both overall and according to reasons for discontinuation from the study).
- The number of participants in the safety and PK analysis sets.

Participant disposition data will be presented in a data listing.

5.2. Protocol Deviations

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 significant or major 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 International Council for Harmonization (ICH) E6(R2) guidelines.

Important protocol deviations will be summarized overall for participants in the safety set. All protocol deviations will be presented in a data listing.

5.3. Inclusion and Exclusion Criteria

Admission criteria deviations will be presented in a data listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

Demographic information collected at screening will be presented in a data listing.

Descriptive statistics will be calculated for the following continuous demographic characteristics collected at screening:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m²)

Frequency counts and percentages will be tabulated for the categorical variables:

- Sex
- Race
- Ethnicity

The summaries will be presented by treatment sequence overall for participants in the safety set.

6.2. Medical History

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version to be delineated in the clinical study report [CSR]) and presented in a data listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Medications that stop prior to the first dose of any study drug will be classified as prior medication. Medications that start on or after the first dose of any study drug will be classified as concomitant. If a medication starts before the first dose of any study drug and stops on or after the first dose of any study drug, then the medication will be classified as both prior and concomitant.

All prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (version to be delineated in the CSR) and presented in a data listing.

7.2. Study Treatment

The study drug administration and drug accountability data as collected on eCRF will be presented in the data listings.

A data listing detailing meal information will also be presented.

8. Safety Analysis

All safety summaries and analyses will be based upon the safety set.

8.1. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A treatment emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in severity or frequency after exposure.

An AE is considered a serious AE (SAE) 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.

The AE's relationship to study treatment will be evaluated by the investigator. The following relationships will be collected on eCRF: probably related, possibly related, or not related. The AEs that are evaluated as probably or possibly related will be considered treatment-related AEs for summary purpose.

The severity of AEs will be classified by the investigator as mild, moderate, or severe, and AEs will also be graded based on Common Toxicity Criteria for Adverse Events (CTCAE) V5.0.

Adverse events of special interest (AESIs) will be identified by the investigator on the eCRF. AESIs include:

- Grade ≥ 2 increased bilirubin
- Grade ≥ 2 increased alanine aminotransferase (ALT)
- Grade ≥ 2 increased aspartate aminotransferase (AST)

An overall AE summary will be generated presenting the frequency and percentage of participants and the number of AEs, by treatment and the overall population, for the following:

- (For Part A Only) Any AE (presented by overall only)
- Any TEAE
- Any TEAE related to Plixorafenib
- Any TEAE related to Cobicistat
- Any Grade ≥ 3 TEAE
- Any SAE
- Any TEAE leading to study drug discontinuation
- Any TEAE leading to early study discontinuation
- Any AESI
- Any Death

All AEs will be coded using MedDRA (version to be delineated in the CSR). The TEAEs will also be summarized, by treatment and overall population, by system organ class (SOC), preferred term (PT), by CTCAE toxicity grade, and either:

- Part A: by Relationship to study treatment.
- Part B: or for related TEAEs only.

Treatment Emergent AESIs will also be presented by SOC and PT, by treatment and overall.

An additional table will summarize the TEAEs by treatment sequence and overall, by SOC and PT.

The TEAE summary tables will be sorted by SOC and PT. System organ class will be displayed alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC. A participant with 2 or more events within the same level of summarization will be counted only once in that level using the highest CTCAE grade, or most related incident (for Part A summary by relationship only). Percentages will be based on the number of participants in the safety set.

All AEs will be presented in a data listing. Separate data listings will be generated for treatment related AEs, AESIs, SAEs, and AEs leading to treatment discontinuation.

For Part A and B, a TEAE will be assigned to the last treatment received prior to the assessment/observation as below:

- Treatment received in Treatment Period 1 if the AE start date/time is on or after the first dose of study drug in the Treatment Period 1, but prior to the first dose of study drug in Treatment Period 2.
- Treatment received in Treatment Period 2 if the AE start date/time is on or after the first dose of study drug in the Treatment Period 2, but prior to the first dose of study drug in Treatment Period 3.
- Treatment received in Treatment Period 3 if the AE start date/time is on or after the first dose of study drug in the Treatment Period 3.

8.2. Clinical Laboratory Evaluations

The following laboratory tests will be performed for Part A and B:

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-glutamyl transferase, 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
Other tests	<p>Serology: Hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antibody types 1 and 2 (screening only)</p> <p>Urine drug screen (alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, cotinine, methamphetamines, methylenedioxymethamphetamine, and opiates [including heroin, codeine, and oxycodone])</p> <p>Female participants: Follicle-stimulating hormone, urine pregnancy test/ serum pregnancy test (human chorionic gonadotropin)</p>

The hematology, serum chemistry, and urinalysis tests will be performed at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in [Section 13](#)).

All clinical laboratory test results will be presented in the data listings. Laboratory values that are outside of the normal reference range will be flagged in the data listings. Laboratory values will

also be graded per CTCAE V5.0, and the resulting grade for abnormal tests will be reported in the data listings.

Clinically significant laboratory test results and their associated adverse events or medical history, as recorded by the investigator on the laboratory eCRF, will be presented in a data listing.

Actual values and change from baseline for hematology and serum chemistry at each time point, and at the maximum and minimum post baseline value will be tabulated by treatment for the safety set.

An additional summary presenting the actual values and change from baseline for hematology and serum chemistry at each time point, and at the maximum and minimum post baseline value, using an alternate definition of baseline will be tabulated. For the summary, baseline will be defined as the last non-missing assessment (including repeat and unscheduled assessment) on or prior to Check-In (Day -1).

8.3. Vital Sign Measurements

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature, and will be measured at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in [Section 13](#)).

All vital sign measurements will be presented in a data listing. The actual values and change from baseline values at each time point, and at the maximum and minimum post baseline value will be tabulated by treatment for the safety population.

8.4. Physical Measurements

All body weight, height, and BMI measurements will be presented in a data listing.

8.5. Physical Examination

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).

Full physical examinations will be performed at screening and check-in, and a symptom driven physical examinations may be performed at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in [Section 13](#)).

All physical examination results will be presented in a data listing.

8.6. Electrocardiograms

Single 12-lead ECGs will be obtained 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. 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.

Heart Rate, RR interval, PR interval, QRS width, QT interval, and QT interval corrected for heart rate using Fridericia's formula (QTcF), and interpretation of ECG will be captured on the eCRF.

Single 12-lead ECG will be performed at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in [Section 13](#)).

All ECG data will be presented in a data listing. The actual values and change from baseline at each time point, and at the maximum and minimum post baseline value, will be tabulated overall for the safety analysis set. For ECG summaries baseline will be defined as the last non-missing assessment (including repeat and unscheduled assessments) prior to the first dose of any study drug.

9. Other Analysis

For the following analysis, the methodology and data handling specifications for this data, if applicable, will be described in a separate analysis document created by the sponsor, *Fore Biotherapeutics*, or their designee.

In Part A only, evaluation of the metabolic profile of plixorafenib in plasma and urine will be conducted and the results will be reported separately.

If feasible, in Part A and B, 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 will be evaluated.

In Part B only, the effect of single dose administration of plixorifenib on endogenous biomarkers such as coproporphyrin may be evaluated.

10. Interim Analysis

No formal interim analyses are planned.

As noted in [Section 1](#), analysis was conducted at the end of Part A to facilitate the decision making process for the requirement and design of Part B of the study.

11. Changes in the Planned Analysis

Any changes from this statistical analysis plan will be documented in the CSR for this study.

The protocol specified that TEAEs were to be summarized by severity. A protocol clarification letter (dated 15th May 2024) was issued explaining that AEs would be coded via CTCAE v5.0. It was determined that examining TEAEs by CTCAE grade was desired rather than severity. As such, TEAEs will be summarized by CTCAE toxicity grade. Severity will still be included in AE listings.

For laboratory results, to examine the potential of a treatment effect being carried into the next treatment period by using a by period baseline (because the predose assessment may be on Day 4 of the treatment period, while the subsequent period starts on Day 8), an additional summary using a baseline result from before any treatment (as described in [Section 8.2](#)) will be created to evaluate any safety signal masked by inducing a carry over effect.

The protocol specified that ECG analysis will include analysis of the actual visit and change from baseline summarized by treatment at each timepoint. However, examining the schedule of assessments, the ECG assessments have no post baseline assessments (except Day 19/EOS) if the definition of baseline specified in a protocol clarification letter (dated 15th May 2024) and this SAP is used. As such, ECG summaries will instead be presented at each timepoint overall only, not by treatment, using a baseline definition as specified in [Section 8.6](#).

The protocol specified TEAEs were to be summarized by relationship to study drug. For Part B, all TEAEs and treatment-related TEAEs will be summarized respectively.

12. References

Department of Health and Human Services, Food and Drug Administration (DHHS), Center for Drug Evaluation and Research (US). Guidance for industry: Assessing the effects of food on drugs in INDs and NDAs — clinical pharmacology considerations. June 2022. [cited 2024 Jan 25] [12 screens] Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerations>

13. Schedule of Assessments

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) Ideal procedural flow for site will be ECG → vital signs → meal (for treatment 3) → blood collection → dosing. When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close

- to the scheduled time window as possible. 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 8.2](#).
 - c) Females only. Further details are provided in Protocol 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.
 - f) Further details on vital signs (respiratory rate, body temperature, pulse rate, and blood pressure) measurements are provided in Protocol Section 6.2.4.
 - g) ECG should be recorded at screening, pre-dose within 2 hours on each dosing day, and at EOS. Further details on ECG recordings are provided in Protocol 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, 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 8.2](#) and Protocol Section 6.2.3
 - i) Further details are provided in Protocol 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 Protocol Section 5.1.
 - l) Further details on the collection of blood samples for PK analysis are provided in Protocol Section 6.1.
 - m) Further details on the collection of urine samples for PK analysis are provided in Protocol Section 6.1.
 - n) Further details on collection and reporting of AEs are provided in Protocol 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 Protocol Section 5.5.1.

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	D 1	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:

- 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).
- A complete list of serology assessments is provided in [Section 8.2](#).
- Females only. Further details are provided in Protocol 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 Protocol Section 6.2.6.
- f) Further details on vital signs (respiratory rate, body temperature, pulse rate, and blood pressure) measurements are provided in Protocol 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 Protocol 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 8.2 and Protocol Section 6.2.3.
- i) Further details are provided in Protocol 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 Protocol Section 5.1.
- l) Further details on the collection of blood samples for PK analysis are provided in Protocol Section 6.1.
- m) Further details on collection and reporting of AEs are provided in Protocol 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 protocol Section 5.5.1.

Statistical Analysis Plan (SAP) Client Approval Form

Client:	Fore Biotherapeutics
Protocol Number:	F8394-101

Document Description:	Final Statistical Analysis Plan
SAP 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 (FORE8394) IN HEALTHY PARTICIPANTS
SAP Version Number:	2
Effective Date:	26 th November 2024


Author(s):

For PPD: Jack Keeler, Lead Statistician

For Fore: Kongming Wang, Executive Director, Statistics
Stacie Shepherd, Chief Medical Officer

Approved by:

Signed by:
Kongming Wang




Signer Name: Kongming Wang
Signing Reason: I approve this document
Signing Time: 26-Nov-2024 | 6:43:56 AM PST
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Kongming Wang, Executive Director, Statistics
Fore Biotherapeutics

Date (DD-MMM-YYYY)

Signed by:
Stacie Shepherd



Signer Name: Stacie Shepherd
Signing Reason: I approve this document
Signing Time: 26-Nov-2024 | 6:01:28 PM PST
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Stacie Shepherd, Chief Medical Officer
Fore Biotherapeutics

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Page 1 of 1
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Page 31