Protocol C4691001

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, SINGLE AND MULTIPLE-DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-07612577 (PF-06264006 [CTB] + PF-07338233 [AVP]) IN HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan
(SAP)

Version: 1.0

Date: 21 Oct 2022

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) is for study C4691001 and is based on Protocol Amendment 1 dated 06-Sep-2022.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 1.0 21 Oct 2022	Protocol Amendment 1 06 Sep 2022	N/A (This is the 1st version of SAP)	N/A

2. INTRODUCTION

This *study is a Phase 1 study of PF-07612577 (PF-06264006 [CTB] + PF-07338233 [AVP]) in approximately 44 healthy adult participants. It is a **2-PART** study combining **PART-1**: Single dose PK, safety and tolerability of various CTB doses alone or when coadministered with AVP, and **PART-2**: Multiple dose PK, safety and tolerability of CTB + AVP coadministered, including optional Japanese and Chinese cohorts.*

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4691001.

2.1. Modifications to the Analysis Plan Described in the Protocol

N/A

2.2. Study Objectives, Endpoints, and Estimands

The below tables list the study objectives with relative endpoints for PART-1 and PART-2 which are copied directly from the protocol. There are no estimands for this study.

PART-1: Single Dose

Type	Objective	Endpoint
	Primary	**Primary**
PK	*To assess the plasma PK profile of CTB following a single dose of CTB alone or in combination with AVP.*	*Plasma PK parameters of cis-CTB:* ▪ *C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn).* ▪ *If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.*
PK	*To assess the plasma PK profile of AVP following administration with single doses of CTB in combination with AVP.*	*Plasma PK parameters of AVP, AVI and HPA:* ▪ *C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn).* ▪ *If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.*
Safety / Tolerability	*To assess the safety and tolerability following a single dose of CTB alone or in combination with AVP.*	▪ *Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs.* ▪ *Frequency and magnitude of abnormal laboratory findings.* ▪ *Changes from baseline in vital sign measurements and 12-lead ECG parameters.*

PART-2: Multiple Dose (including optional Japanese and Chinese Cohorts)

Note: In addition to PART-2, the below table (directly extracted from Protocol Amendment 1) also includes some tertiary/exploratory objectives for PART-1.

Type	Objective	Endpoint
	Primary	**Primary**
PK	*To assess the plasma PK profile of cis-CTB and trans-CTB[a] following multiple doses of CTB in combination with AVP.*	*Plasma PK parameters of cis-CTB and trans-CTB[a] on Day 1 (fed, single dose), Day 6 (fed, steady state) and Day 7 (fasted, steady state):* ▪ *C_{max}, T_{max}, AUC_{tau}, $C_{max}(dn)$, $AUC_{tau}(dn)$.* ▪ *If data permit, $t_{½}$, V_z/F, and CL/F.*
PK	*To assess the plasma PK profile of AVP following multiple doses of CTB in combination with AVP.*	*Plasma PK parameters of AVP, AVI and HPA on Day 1 (fed, single dose), Day 6 (fed, steady state) and Day 7 (fasted, steady state):* ▪ *C_{max}, T_{max}, AUC_{tau}, $C_{max}(dn)$, $AUC_{tau}(dn)$* ▪ *If data permit, $t_{½}$, V_z/F, and CL/F.*
Safety / Tolerability	*To assess the safety and tolerability following multiple doses of CTB in combination with AVP.*	▪ *Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs.* ▪ *Frequency and magnitude of abnormal laboratory findings.* ▪ *Changes from baseline in vital sign measurements and 12-lead ECG parameters.*
	Secondary	**Secondary**
PK	*To assess the urinary PK[b] profile of cis-CTB, trans-CTB[a], AVP, AVI and HPA on Day 6 following multiple doses of CTB in combination with AVP.*	*cis-CTB, trans-CTB[a], AVP, AVI and HPA urinary PK parameters (if data permit):* ▪ *Ae_{tau} and Ae_{tau}%, CL_r.*
PK	*To assess PK profile of CTB and AVP when administered in combination in Japanese and Chinese participants.*	*Plasma PK parameters of cis-CTB, AVP, AVI and HPA on Day 1 (fed, single dose), Day 6 (fed, steady state) and Day 7 (fasted, steady state) in Japanese and Chinese cohorts:* ▪ *C_{max}, T_{max}, AUC_{tau}, $C_{max}(dn)$, $AUC_{tau}(dn)$.* ▪ *If data permit, $t_{½}$, V_z/F, and CL/F.*
	Tertiary/ Exploratory	**Tertiary/ Exploratory**
PK	CCI [redacted]	
PK	*To explore the effect of food on PK of cis-CTB, trans-CTB, AVP, AVI and HPA.*	*In PART-2, comparison of plasma PK parameters of cis-CTB, trans-CTB, AVP, AVI and HPA on Day 6 (fed) versus Day 7 (fasted).*
PK	*To explore the potential drug-drug interaction when CTB and AVP are co-administered.*	*In PART-1, comparison of plasma PK parameters of cis-CTB and trans-CTB after administration of Dose 2 (800 mg CTB + 1350 mg AVP) versus after Dose 3 (800 mg CTB alone).*
Safety / Tolerability	*To determine the potential effect of CTB on cardiac repolarization, if data permit.*	*In PART-1, if supratherapeutic concentrations are achieved, C-QT modeling will be*

		conducted to assess potential effect of CTB on QTc prolongation.

a. *trans-CTB will be measured only in Cohort 2 PART-2.*
b. *cis-CTB, trans-CTB, AVP, AVI and HPA in urine will be measured on Day 6 only in Cohort 2, PART-2.*
CCI [redacted]

2.3. Study Design

2.3.1. Overall Design

This study will consist of PART-1: Single dose and PART-2: Multiple dose, including optional Japanese and Chinese cohorts. PART-1 and PART-2 are randomized, double-blind (participant and investigator blinded and sponsor open) cohorts.

In PART-1 and PART-2, treatment sequences and the dosing regimen may be adjusted during the study based on emerging safety, tolerability, and PK data. The provisional dosing regimens for Parts 1 and 2 are provided in Table 6 and Table 7 of the Protocol Amendment (06 Sep 2022)*, respectively. Except D1 in PART-1, all other dose levels and/or meal condition may be changed based on emerging PK, safety, and tolerability data. Dose escalation of CTB (and AVP, when applicable) to higher doses will be based on all available (a minimum of 24 hours post-dose) safety data in a minimum of 5 participants (4 active and 1 placebo) at the previous dose levels of CTB and/or AVP. AVP dose for PART-1 may be 900 mg, 1350 mg, or 1800 mg (in Period 5 only) as long as PK exposures for AVI in the next higher cohort are not projected to be higher than PK stopping limit (AVI AUC ≤ 354 µg.hr/ml- NOAEL in the 14-day pivotal repeat-dose toxicology study in rats). In PART-2, at least 6 days of safety data in a minimum of 5 participants (4 active and 1 placebo) from Cohort 2 will be reviewed prior to proceeding to optional Cohorts 3, 4, 5 and/or 6.*

PART-1: Single Dose

PART-1 will include 1 cohort and up to 5 periods with approximately 8 participants in total. This part will have a randomized, double-blind (sponsor-open), 5-period, sequential single dose design. Periods 4 and 5 are optional and may be used to further explore PK at additional doses, based on emerging PK data. In each period, approximately 6 participants will receive a single oral dose of CTB or CTB and AVP combined, and approximately 2 participants will receive the matching placebo under fed state. Each participant may receive either a single dose of CTB, CTB and AVP combined, or matching placebo during each period. In each period, participants on active treatment will receive D1, D2, D3, D4 (optional), or D5 (optional) dose levels, respectively. There will be a washout interval of a minimum of 3 days between doses for a given participant. Participants will be required to stay at the CRU for the duration of the washout interval.

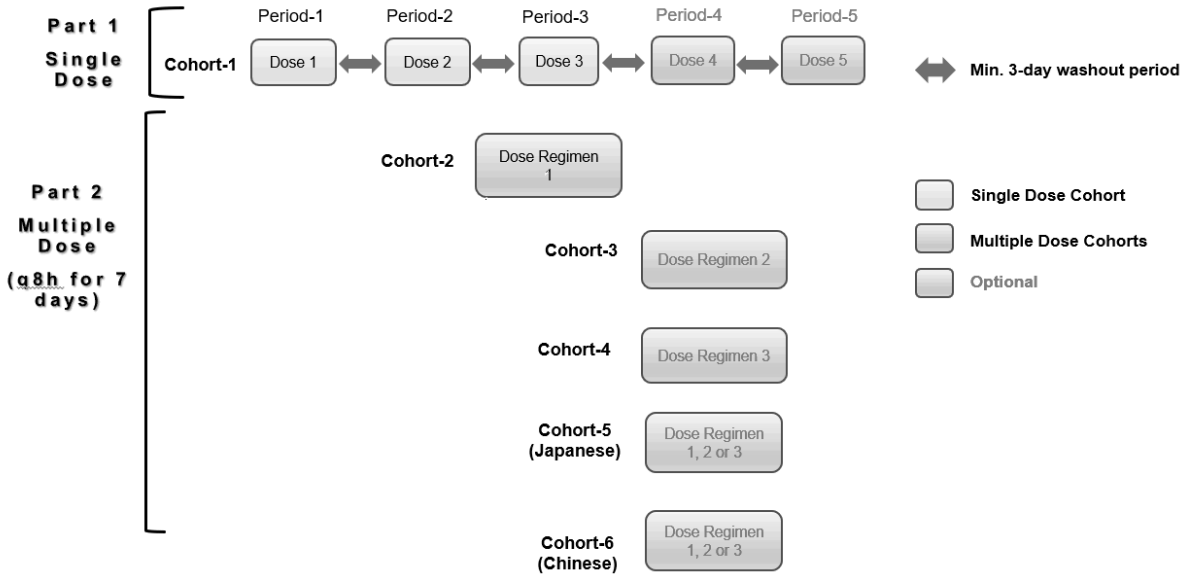
PART-2: Multiple Dose

PART-2 will include up to 5 cohorts, ie, Cohort 2, and up to 4 optional cohorts including optional Cohort 5 (Japanese Cohort) and optional Cohort 6 (Chinese Cohort) with

approximately 8 participants each in Cohorts 2, 3 and 4, and six participants each in Cohorts 5 and 6, and up to approximately 36 participants planned in total. This part will have a randomized, double-blind (sponsor-open), sequential multiple-dose design. In Cohorts 2,3 and 4, approximately 6 participants will receive 1 of the dose regimens of CTB and AVP combined, and approximately 2 participants will receive the matching placebo orally under fed state (except Day 7 which will be administered fasted). In Cohorts 5 and 6, approximately 5 participants will receive 1 of the dose regimens of CTB and AVP combined and approximately 1 participant will receive the matching placebo orally under fed state (except Day 7 which will be administered fasted.) From Day 1 to Day 7, CTB and AVP combined or the matching placebo will be administered q8h (ie, TID), with the dose regimen of DR1 (for Cohort 2), DR2 (for optional Cohort 3), DR3 (for optional cohort 4) and either DR1, DR2 or DR3 (for Cohort 5, optional Japanese Cohort and Cohort 6, optional Chinese Cohort).

Figure 1 shows the study schema indicating the two parts and the details on dosage.

Figure 1. C4691001 Study Design



PART-1: *Dose 1 = 400 mg CTB + 900 mg AVP; Dose 2 = 800 mg CTB + 1350 mg AVP; Dose 3 = 800 mg CTB alone; Dose 4 = 1200 mg CTB + 1350 mg AVP*; Dose 5 = 1600 mg CTB alone or 1200 mg CTB + 1800 mg AVP.*

PART-2: *DR1 = 400 mg CTB + 1350 mg AVP* q8h for 7 days; DR2 = 400 mg/800 mg CTB + 1350 mg AVP* q8h for 7 days; DR3 = 800 mg/1200 mg CTB + 1350 AVP q8h for 7 days.*

** 1350 mg AVP may be replaced with 900 mg AVP, based on safety, tolerability and PK data.*

Note that except Dose 1 in PART-1, all other dose levels and/or meal condition may be changed based on emerging PK, safety, and tolerability data.

2.3.2. Number of Participants

Up to 44 participants (8 in PART-1 and 36 in PART-2) will be randomly assigned to study intervention.

In **PART-1**, *a sample size of approximately 8 participants (6 active, 2 placebo) for this single-cohort, cross-over study has been chosen based on the need to minimize first exposure of healthy participants to CTB + AVP and the requirement to provide adequate safety and tolerability information and PK information at each dose level.*

In **PART-2,** *approximately 36 participants (8 participants each in Cohorts 2, 3 and 4: six on CTB + AVP, 2 on matching placebo and 6 participants each in Cohorts 5 and 6: five on CTB + AVP, 1 on matching placebo) for this 5-cohort (1 cohort and 4 optional cohorts) multiple dose study has been selected to provide adequate PK, safety and tolerability information. This sample size has been judged sufficient to obtain a preliminary evaluation of safety, tolerability, and PK data in these populations.*

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Section 2.2 lists the study objectives and endpoints for PART-1 and PART-2. The primary endpoints of PART-1 and PART-2 are related to safety/tolerability and plasma PK endpoints. These are described futher in Section 3.5.

The definition and additional details of the PK parameters for PART-1 and PART-2 are provided in Table 2 and 3, respectively.

3.2. Secondary Endpoint(s)

The secondary endpoints are only for PART-2 and they include *urinary PK endpoints* as well as the *plasma PK endpoints* for *Japanese and Chinese participants.*

3.3. Other Endpoints

Tertiary/exploratory objective/*endpoint includes effect of food on plasma PK of cis-CTB, trans-CTB, AVP, AVI and HPA. Tertiary endpoint in Cohort 2 PART-2 includes* CCI [redacted] *Tertiary endpoints such as* CCI [redacted] *in PART-2 and C-QT modeling may not be reported in the CSR and may be reported separately.* In PART-1, *to explore the potential drug-drug interaction when CTB and AVP are co-administered*, tertiary endpoint also includes *comparison of plasma PK parameters of cis-CTB and trans-CTB after administration of Dose 2 versus after Dose 3.*

The *PK parameters for cis-CTB, trans-CTB, AVP, AVI and HPA will be derived (if data permit) from the concentration-time data using standard noncompartmental methods following a single oral dose (*Table 2*) and multiple oral doses (*Table 3*). Urine cis-CTB, trans-CTB, AVP, AVI and HPA PK parameters are described in* Table 3. *Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling*

times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 2. ***Plasma cis-CTB, AVP, AVI, and HPA PK Parameters for PART-1: Single Doses***

Parameter	Analysis Scale	**PF-07612577 (or** PF-06264006***)**
AUC_{last}	Ln	D, A
AUC_{inf}[a]	Ln	D, A
C_{max}	Ln	D, A
T_{max}	R	D
$t_{½}$[a]	Ln	D
CL/F[a]	Ln	D
V_z/F[a]	Ln	D
AUC_{last}(dn)	Ln	D
AUC_{inf}(dn)[a]	Ln	D
C_{max}(dn)	Ln	D

* Note that Dose 3 in PART-1 is PF-06264006 (CTB) only
D=display with descriptive statstics,
R=raw (untransformed),
Ln=natural-log transformed
A=analyzed
dn=dose normalized to a 1 mg dose.
a. If data permit

Table 3. ***Plasma and Urine cis-CTB, trans-CTB, AVP, AVI and HPA PK Parameters for PART-2: Multiple Doses***

Plasma		
Parameter	**Analysis Scale**	**PF-07612577**
AUC_{tau}	Ln	D, A
C_{max}	Ln	D, A
T_{max}	R	D
C_{min}	R	D
PTR	Ln	D
R_{ac}	Ln	D
$R_{ac,Cmax}$	Ln	D
CL/F[a]	Ln	D
$t_{½}$[a]	R	D
V_z/F[a]	Ln	D
AUC_{tau}(dn)	Ln	D
C_{max}(dn)	Ln	D
Urine		
Parameter	**Analysis Scale**	**PF-07612577**
Ae_{tau}	R	D
Ae_{tau}%	R	D
CL_r	R	D

D=display with descriptive statstics,
R=raw (untransformed),
Ln=natural-log transformed
A=analyzed
dn=dose normalized to a 1 mg dose.
a= If data permit

3.4. Baseline Variables

Baseline variables are those collected prior to dosing on Day 1 or before Day 1.

Baseline for laboratory data, vital signs and ECG are defined in sections 3.5.2, 3.5.3 and 3.5.4 respectively.

3.5. Safety Endpoints

Safety endpoints include:

- *Adverse events (AEs) and serious adverse events (SAEs),*
- *Vital signs,*
- *Electrocardiograms (ECG),*

- *Laboratory data,*

3.5.1. Adverse Events and Serious Adverse Events

Active collection period of AEs and SAEs *for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.*

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the end of the study will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

A 3-tier approach for summarizing AEs will not be used due to the low number of participants planned to be recruited.

3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol.

For PART-1, baseline will be the last pre-dose measurement prior to dosing in each study period. For PART-2, baseline will be the last pre-dose measurement prior to dosing on Day 1.

Clinically significant abnormal laboratory test findings will be *those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 24 hours after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.*

3.5.3. Vital Signs

Supine BP and pulse will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest.

For PART-1, baseline will be the last pre-dose measurment prior to dosing on Day 1 in each study period. For PART-2, baseline will be the last pre-dose measurement prior to dosing on Day 1.

The following vital signs endpoints will be determined:

- Change from baseline for all measurements taken post-dose
- The maximum increase from baseline over all measurements taken post-dose

- The maximum decrease from baseline over all measurements taken post-dose

The maximum increase from baseline will be calculated by first subtracting the baseline value from each post-dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

Similarly, the maximum decrease from baseline will be determined by selecting the minimum value of the changes from baseline. In cases where a participant does not show a decrease, the minimum increase should be taken.

3.5.4. Electrocardiogram (ECG)

ECG values of potential clinical concern are listed in Appendic 8 of the protocol. *Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip)* should be collected at time detailed in the SoA given in the protocol to *automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. They should be performed after the participant has rested quietly for at least 5 minutes in a supine position.*

For PART-1, *all ECGs are collected in triplicate, except at screening.* Baseline will be defined as the average of the triplicate measurements prior to dose administration on Day 1 in each study period.

For PART-2, *baseline* will be defined as *the average of the triplicate ECG measurements collected at 3 time points prior to dose administration on Day 1* where *triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart*.

The following ECG endpoints will be determined:

- Change from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS complex.

- The maximum absolute value (post-dose) will be calculated for QTcF, PR and QRS.

- The maximum increase from baseline over all measurements taken post-dose will be calculated for QTcF.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each triplicate-average post-dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

3.6. Other Endpoint(s)

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures. For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	***Description***
Enrolled	*"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
Full Analysis Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.*
Safety Analysis Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.*
PK Concentration Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported for the given part of the study.*
PK Parameter Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest are reported for the given part of the study.*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no statistical hypotheses or decision rules.

5.2. General Methods

In general, the data from each part of the study will be analysed and accordingly report in a single CSR which will be issued at the end of the study. Where appropriate, graphical representatios will be used to summarize some of the measurments by treatment and visits.

5.2.1. Analyses for Continuous Endpoints

Continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, cv%, median, minimum and maximum values.

Log transformed continuous variables will be presented using summary statistics: number of observations, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

5.2.2. Analyses for Categorical Endpoints

Categorical variables will be presented using summary statistics: number of observations and percentages.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data:

The sponsor data standard rules for imputation will be applied for the analysis of the safety endpoints.

5.3.2. Pharmacokinetic (PK) Data:

To handle the missing PK data the following methods will be implied:

PK Parameters:

If a PK parameter cannot be measured, the parameter will be coded as “Not Calculated”. This values will be set to missing when the summary tables are to be calculated. If a subject discontinues the trial, the “Not Calculated” values won’t be generated after the day of discontinuation.

If the PK parameter has a known biased estimated because of any unexpected event before the complete absorbtion, a footnote in the summary tables will be created to mention that. The statistical analysis and the summary tables won’t include these values.

Concentrations Below the Limit of Quantification:

Concentrations below the limit of quantification (BLQ) for all data presentations (except listings) will be set to 0. For listings, BLQ will be reported as “< Lower Limit Quantifcation (LLQ)”.

Anamalous, Deviations and Missing Concentration:

If one of the folowings happens then the statistics will be calculated having set concentrations to missing in summary tables and plots of median profiles:

1. A deviation in sampling time is concerning or a concentration has been flagged anomalousely by pharmacokineticists.

2. A concentration has been collected as “Not Done” or “No Sample”.

6. ANALYSES AND SUMMARIES

This section describes the analyses planned for endpoints that are either primary for PART-1 and PART-2, or secondary and tertiary/exploratory for PART-2.

Separate tables will be produced for **PART-1: Single Dose** and **PART-2: Multiple dose**, unless otherwise specified. In PART-2, Japanese and Chinese will be separate groups.

6.1. Primary Endpoint(s)

This section describes the analyses planned for the primary endpoints which include the pharmacokinetics of PF-06264006 (CTB) and PF-07338233 (AVP) in PART-1 and PART-2.

6.1.1. PK Data

- Response based on plasma concentrations in PART-1 and PART-2.
- Population: PK Parameter Set
- Statistical methods:
    - *Plasma concentrations*: *Will be listed and summarized descriptively by nominal* PK *sampling time and treatment*.
    - *Individual participant and median profiles of the concentration-time: Will be plotted by treatment* by the use of *actual PK sampling time*.
    - Median profiles: *Will be presented on both linear-linear and log-linear scales.*
    - PK parameters listed in Tables 11 and 12 of the protocol: *Will be summarized descriptively by dose.*
    - PART-1 dose normalized: *Will be plotted against dose (using a logarithmic scale) and will include individual participant values as well as the geometric means for each dose.*

Missing values will be handled as described in Section 5.3. Each PK parameter will be presented by time and treatment and have the following set of summary statistics:

Parameter	Parameters	Summary Statistics
Primary (Plasma PK)	C_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn). If data permit, AUC_{inf}, AUC_{inf}(dn), V_z/F, and CL/F.	N, Mean (arithmetic), Median, Standrad Deviation (SD), Minimum, Maximum, Percentage of Coefficient of Variation, Geometric Mean, Geometric Coefficient of Variation.
Primary (Plasma PK)	T_{max}	N, Median, Minimum, Maximum
Primary (Plasma PK)	If data permit, $t_{½}$	N, Mean (arithmetic), Median, Percentage of Coefficient of Variation, Minimum, Maximum

6.2. Secondary Endpoint(s)

This section describes the analyses planned for the secondary endpoints which include the PK of PF-06264006 (CTB) and PF-07338233 (AVP) in PART-2.

6.2.1. PK Data

- Response based on urinary concentrations in PART-2.
- Population: PK Parameter Set
- Statistical methods:
    - *PART-2, urine amounts of CTB and AVI: Will be listed and summarized descriptively.*
    - *PART-2 plasma PK parameters for Japanese and Chinese participants*: *Will be compared to Western participants.*

Missing values will be handeled as described in Section 5.3. Each PK parameter will be presented by time and treatment and have the following set of summary statistics:

Parameter	Parameters	Summary Statistics
Secondary (Urinary)	Ae_{tau} and Ae_{tau}%, CL_r	N, Mean (arithmetic), Median, Standrad Deviation (SD), Minimum, Maximum, Percentage of Coefficient of Variation, Geometric Mean, Geometric Coefficient of Variation.
Secondary (Japanese and Chinese Participants)	C_{max}, AUC_{tau}, C_{max}(dn), AUC_{tau}(dn). If data permit, V_z/F, and CL/F.	N, Mean (arithmetic), Median, Standrad Deviation (SD), Minimum, Maximum, Percentage of Coefficient of Variation, Geometric Mean, Geometric Coefficient of Variation.
Secondary (Japanese and Chinese Participants)	T_{max}	N, Median, Minimum, Maximum
Secondary (Japanese and Chinese Participants)	If data permit, $t_{½}$	N, Mean (arithmetic), Median, Percentage of Coefficient of Variation, Minimum, Maximum

To assess the relationship between the PK parameters and dose, dose normalized C_{max}, AUC_{last}, and AUC_{inf} (**PART-1**) and C_{max} and AUC_{τ} (**PART-2**) of each of the individual analytes- cis-CTB, trans-CTB, AVI will be plotted against dose (using a logarithmic scale), and will include individual participant values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. In PART-2, the data from the Japanese and Chinese subjects will be identified by different symbols/colours. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented. All dose normalized parameters will be listed along with other individual PK parameters.

Supporting data from the estimation of $t_{½}$ will be listed by treatment and dose where applicable: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. These data may be included in the CSR.

Presentations for each of the individual analytes- cis-CTB, trans-CTB, AVP, AVI and HPA concentrations will be presented using participants in the PK Concentration Set and will include:

- a listing of all concentrations sorted by participant ID, dose, matrix and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- a summary of concentrations by dose and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- individual concentration-time plots by dose (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each dose per scale).

- individual concentration-time plots by participant (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each dose per scale).

- median concentration-time plots (on both linear and semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose).

- mean concentration-time plots (on both linear and semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose).

The scale used for the x-axis (time) of these plots will be decided on review of the data, and will depend on how long PF-07612577 concentration is quantifiable in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

For **PART-2**, urine amounts of PF-07612577 will be listed and summarized descriptively, if data permit.

6.3. Exploratory Endpoints

This section describes the analyses planned for the exploratory endpoints in PART-2.

- Response based on plasma concentrations in PART-1 and PART-2.

- Population: PK Parameter Set

- Statistical methods:

    - *PART-1, drug interaction defined as treatments "800 mg CTB + 900/1350 mg AVP" (Test) versus "800 mg CTB alone" (Reference): For those participants receiving both treatments (Test, Reference), natural log transformed* AUC_{inf}, AUC_{last}, and C_{max} for cis-CTB and trans-CTB *will be analyzed using a mixed effect model with treatment included as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.*

- *PART-2, food effect evaluation defined as fed PK on Day 6 (Test) versus fasted PK on Day 7 (Reference): For those participants* with PK measured in both the fed and fasted states *(Test, Reference)*, *natural log transformed* Cmax and AUCtau for cis-CTB, trans-CTB, AVP and AVI *will be analyzed using a mixed effect model with treatment* (i.e. fed-state) *included as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.*

6.4. Baseline and Other Summaries and Analyses

*Medical history and PE and neurological examination information, as applicable, collected during the course of the study will be considered source data and will **not** be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported*.

6.4.1. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition by treatment. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the sponsor reporting standards.

6.4.2. Demographic Data

Demographic data will be summarised for PART-1, by cohort for PART-2, and overall (if applicable) in accordance with the sponsor reporting standards.

6.4.3. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be reported according to current sponsor reporting standards.

6.5. Safety Summaries and Analyses

- Response based on safety/tolerability in PART-1 and PART-2.
- Population: Safety Analysis Set

6.5.1. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

6.5.2. Laboratory Data

Lab data will be summarized and listed by treatment in accordance with the sponsor reporting standards. Baseline is defined in Section 3.5.2.

6.5.3. Vital Signs

Absolute values and changes from baseline in supine sysolic and diastolic blood pressure, pulse rate, temperature and respiratory rate will be summarized by treatment and time post-dose, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is defined in Section 3.5.3.

Mean changes from baseline for supine systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate will be plotted against time post-dose. Each part will have its own output with 1 line for each treatment. Placebo will be pooled in the plots for PART-2, although the Japanese/Chinese placebo may be plotted separately. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum decrease from baseline for supine systolic and diastolic blood pressures and respiratory rate and maximum increase from baseline for supine pulse rate and temperature will be summarized by treatment, according to sponsor reporting standards.

Minimum and/or maximum absolute values and changes from baseline for supine vital signs will also be summarized descriptively by treatment using categories as defined in Appendix 1. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time points will be counted in these categorical summaries.

6.5.4. Electrocardiograms

Changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated. The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the categories (See Appendix 1) *will be tabulated by treatment. If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the time-matched baseline triplicate values on Day -1, or the average of the predose triplicate values on Day 1.*

C-QT modeling/analysis may be conducted if data permit, and will be reported in a separate report.

7. INTERIM ANALYSES

No interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

APPENDICES

Appendix 1. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value of QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤60	>60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120