Protocol C5091013

A PHASE 1, OPEN-LABEL, RANDOMIZED, SINGLE DOSE, CROSSOVER STUDY TO ESTIMATE THE RELATIVE BIOAVAILABILITY OF PF-07817883 FOLLOWING ORAL ADMINISTRATION OF NEW FORMULATIONS RELATIVE TO THE REFERENCE FORMULATION IN HEALTHY ADULT PARTICIPANTS UNDER FASTED CONDITION

Statistical Analysis Plan
(SAP)

Version: **1**

Date: 22 NOV 2023

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 22 Nov 2023	Original 24 Aug 2023	N/A	N/A

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C5091013.

This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Text in *italics* is taken directly from the protocol.

2.1. Modifications to the Analysis Plan Described in the Protocol

No modifications.

2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint	Estimand
Primary:			
PK (Section 3.1)	*To determine the oral bioavailability of test oral formulations of PF-07817883 relative to the reference oral formulation.*	*Cmax and AUCinf if data permit, otherwise AUClast.*	N/A
Secondary:			
Safety (Section 3.1)	*To evaluate the safety and tolerability of PF-07817883 formulations in healthy participants.*	*Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.*	N/A
Tertiary/Exploratory:			
PK (Section 3.4.1)	*To characterize the PK of PF-07817883 after single oral dose of PF-07817883 formulations.*	*Plasma PK parameters: Tmax, C_{12}, and if data permit Vz/F, CL/F and t½.*	N/A
Other (Section 3.4.2)	*To assess the drug product acceptability of PF-07817883 formulations.*	*Assessment of drug product acceptability via a questionnaire.*	N/A

2.3. Study Design

This is a Phase 1, open-label, randomized, 4-period, 4-sequence crossover study in healthy adult participants evaluating the rBA of 3 new PF-07817883 test oral formulation(s) compared to PF-07817883 reference oral formulation. Approximately 12 participants will be enrolled in this study with approximately equal number of participants randomized to 1 of 4 sequences (Table 2). The new formulations used for each treatment as defined in Table 2 will be decided based on the availability of new formulations.

A sample size of approximately 12 participants with 8 completers was chosen to provide adequate precision to compare the relative bioavailability of test formulations of PF-07817883 relative to the reference formulation in Periods 1 through 4.

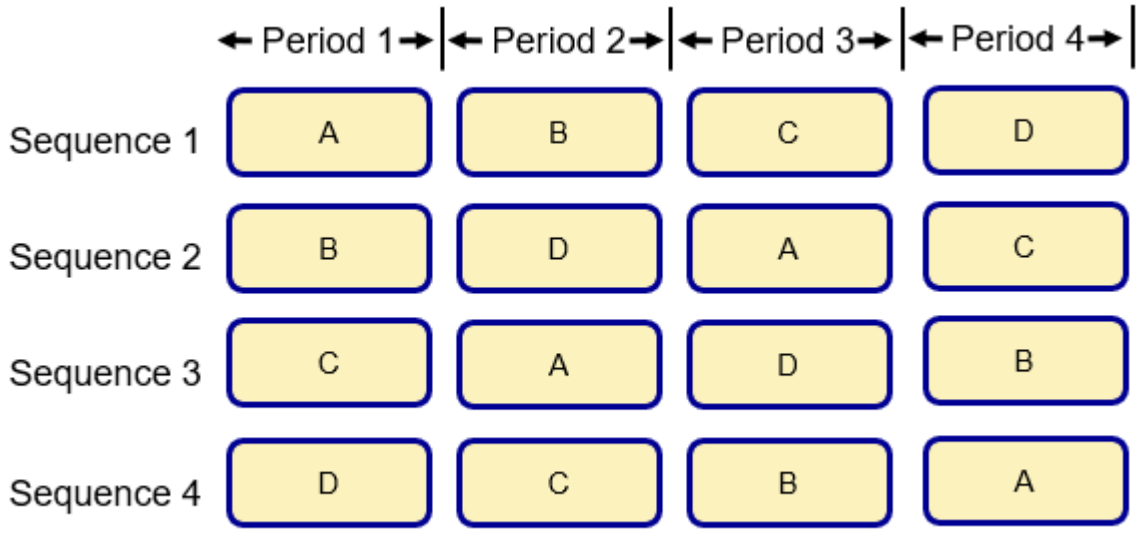
A sample study design schematic is presented in Figure 1.

Table 2. Study Design

Sequence	***Period 1***	***Period 2***	***Period 3***	***Period 4***
1 (n=3)	*A*	*B*	*C*	*D*
2 (n=3)	*B*	*D*	*A*	*C*
3 (n=3)	*C*	*A*	*D*	*B*
4 (n=3)	*D*	*C*	*B*	*A*

Treatment A = PF-07817883 300 mg reference formulation, fasted, DP-006067, 23-DP-01449
Treatment B = PF-07817883 300 mg test formulation 1, fasted, DP-006067, 23-DP-01526
Treatment C = PF-07817883 300 mg test formulation 2, fasted, DP-006973, 23-DP-01687
Treatment D = PF-07817883 300 mg test formulation 3, fasted, DP-006974, 23-DP-01696

Figure 1. Schema



DMID, lot numbers:
A: DP-006067, 23-DP-01449
B: DP-006067, 23-DP-01526
C: DP-006973, 23-DP-01687
D: DP-006974, 23-DP-01696

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Blood samples for PK analysis of PF-07817883 will be taken according to the SoA in the protocol.

Plasma PK parameters of PF-07817883 will be derived (as data permit) from the concentration-time data using standard noncompartmental methods as outlined 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 3. Summary of PF-07817883 plasma PK parameters to be calculated.

Parameter	Definition	Method of Determination	Analysis Scale	Analysis Method
*AUC_{inf}**	*Area under the concentration-time curve from time 0 extrapolated to infinity*	*AUC_{last} + (C_{last}*/k_{el}), where C_{last}* is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis*	ln	A, D
AUC_{last}[a]	*Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}).*	*Linear/Log trapezoidal method.*	ln	A, D
C_{max}	*Maximum observed concentration*	*Observed directly from data*	ln	A, D

*If data permit.
a. 48h PK sample in Periods 1 to 3 will be considered 0h PK sample for the subsequent period.
Abbreviations: A=analyzed using a statistical model (if applicable); D=displayed with descriptive statistics as outlined in Table 5 in Section 6.1; ln=natural-log transformed;.

3.2. Secondary Endpoint(s)

Secondary endpoints include assessment of adverse events (AEs), clinical safety laboratory abnormalities, vital signs and ECG parameters.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- adverse events,
- laboratory data (except data from screening visit),
- vital signs data,
- ECG results

3.2.1. Adverse Events

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 dose of study intervention, 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.

Events that occur in a non-treatment period (e.g., washout or follow-up) will be counted as treatment emergent and attributed to the most recent treatment taken.

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

3.2.2. Clinical Safety Laboratory Data

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

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are 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.

Baseline will be the measurement taken on Day -1.

To determine if there are any clinically significant laboratory abnormalities, the hematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

3.2.3. Vital Signs Data

Single supine blood pressure and pulse rate measurements will be taken at times detailed in the SoA given in the protocol.

Baseline for these measures will be defined as the last pre-dose measurement in each study period.

The following endpoints will be determined:

- Change from baseline (CFB) in systolic and diastolic BP and pulse rate
- The minimum and maximum post-dose systolic and diastolic BP and pulse rate
- The maximum increase and decrease from baseline over all measurements taken post-dose for systolic and diastolic BP and pulse rate

The maximum increase from baseline will be calculated by selecting the maximum change from baseline over the respective period, 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 change from baseline. In cases where a participant does not show a decrease, the minimum increase should be taken.

If 3 of more participants have unplanned measurements at the same timepoint these may be summarized in addition to the planned timepoints.

3.2.4. Electrocardiogram Data

A single 12-lead ECG will be obtained on all participants at times detailed in the SoA given in the protocol. ECG endpoints include heart rate, QT interval, PR interval and QTcF and QRS

complex. If not supplied QTcF will be derived using Fridericia's heart rate correction formula [1]:

$$QTcF\ (msec) = QT\ (msec) / (RR)^{1/3} \quad \text{where RR (sec)} = 60/HR \text{ (if RR not provided).}$$

Baseline will be defined as the last measurement prior to administration of study treatment on Period 1 Day 1.

The following endpoints will be determined:

- Change from baseline in QT, QTcF, PR, QRS interval and heart rate
- The maximum post-dose QTcF, heart rate, PR and QRS interval
- The maximum increase from baseline over all measurements taken post-dose for QTcF, heart rate, PR and QRS values

The maximum increase from baseline will be calculated by selecting the maximum change from baseline over the respective period, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

3.3. Other Safety Endpoint(s)

Not applicable

3.4. Other Endpoint(s) (or, Exploratory Endpoints)

3.4.1. Additional Plasma PK Parameters

Additional plasma PF-07817883 PK parameters, as described in Table 4, will be determined:

Table 4. Additional PF-07817883 Plasma PK Parameters

Parameter	Definition	Method of Determination	Analysis Scale	Analysis Method
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence	R	D
C_{12}	Concentration observed at 12 hours	Observed directly from data	ln	D
V_z/F*	Apparent volume of distribution	$Dose/(AUC_{inf} \times k_{el})$	ln	D
CL/F*	Apparent clearance	$Dose/AUC_{inf}$	ln	D
$t_{½}$*	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.	R	D

Table 4. Additional PF-07817883 Plasma PK Parameters

Parameter	Definition	Method of Determination	Analysis Scale	Analysis Method

*=if data permits.
Abbreviations: D=displayed with descriptive statistics as outlined in Table 5 in Section 6.1; ln=natural-log transformed; R = raw (untransformed).

3.4.2. Drug Product Acceptability

The acceptability attributes of PF-07817883 will be evaluated by the participant using a Drug Product Acceptability Questionnaire (as shown in Appendix 8 of the protocol). *In each period, each participant will complete the Drug Product Acceptability Questionnaire immediately following dosing.*

Each item will be evaluated on a Likert scale with numeric categories to capture the level of agreement or disagreement with a statement about drug-product appearance, palatability, swallowability, or overall impression of taking the drug product (1=strongly agree, 5=strongly disagree). The frequency of each response for each item will be summarized and reported.

3.5. Baseline Variables

Not applicable

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.

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.*
Safety analysis set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention in at least one treatment period. Participants will be analyzed according to the product they actually received.*
PK Concentration analysis set	*The PK concentration population is defined as all participants randomized and treated who have at least 1 concentration value in at least 1 treatment period.*

Participant Analysis Set	Description
PK Parameter analysis set	*The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PK parameters of interest in at least 1 treatment period.*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing planned for this study, and no statistical decision rules will be applied.

5.2. General Methods

Unless otherwise stated, all summaries and plots will be presented by treatment.

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.

5.2.3. Mixed Effects Model

A mixed effects model with sequence, period and treatment as fixed effects and participant within sequence as a random effect will be used.

Estimates of the adjusted (least squares) mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment A will be the Reference treatment while Treatments B, C, and D will be the Test treatments.

The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and the Kenward-Roger degrees of freedom algorithm.

Residuals from the models will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals, but these will not be included in the clinical study report. If there are major deviations from normality or outliers (where studentized [conditional] residuals are greater than 3 or less

than -3), then the effect of these on the conclusions may be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study if applicable.

Example code is shown in Appendix 1.

5.3. Methods to Manage Missing Data

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

5.3.1. Concentrations Below the Limit of Quantification

In all PK data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In listings, BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification (LLQ).

5.3.2. Deviations, Missing Concentrations and Anomalous Values

For PK summary tables and plots of mean/median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (i.e., not done) or NS (i.e., no sample),
2. A deviation in sampling time (10% deviation within 10 hours following dosing) is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist/statistician.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (i.e., not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues). In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

If an individual participant has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

6. ANALYSES AND SUMMARIES

For all presentations, study day will refer to the day within a particular treatment period, unless otherwise specified.

6.1. Primary Endpoint(s)

Plasma PK parameters for PF-07817883, as described in Section 3.1 and the additional plasma PK parameters listed in Section 3.4.1, will be listed and summarized descriptively by treatment, as applicable, for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

Each PK parameter will be summarized by treatment using the summary statistics as specified in the table below:

Table 5. Summary Statistics for PF-07817883 Plasma PK Parameters

	Parameter	Summary Statistics
Primary	AUC_{last}, AUC_{inf}*, and C_{max}	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum, geometric mean and geometric CV%.
Tertiary	T_{max}	N, median, minimum, maximum.
	$C_{12,}$ V_z/F*, and CL/F*	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum, geometric mean, and geometric CV%.
	$t_{½}$*	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum.

*: if data permit

Supporting data from the estimation of AUC_{inf} and $t_{½}$ will be listed by treatment: 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}. This data may be included in the clinical study report.

For AUC_{inf} (if data permit), AUC_{last}, and C_{max}, a listing of the individual participant ratios (test/reference) will be provided. Box and whisker plots for AUC_{inf} (if data permit), AUC_{last}, and C_{max}, will be plotted by treatment and overlaid with geometric means.

The following will be presented for the plasma concentration data using the PK Concentration Set (as defined in Section 4):

- a listing of all concentrations sorted by participant ID 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 nominal PK sampling time and treatment. 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.

- mean and median concentration time plots (on both linear and semi-log scales) against nominal time post-dose by treatment. One plot for each scale will be presented, which will include all doses in the same plot colored by treatment.

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

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-07817883 concentration is quantifiable in the matrix.

The nominal PK sampling time will be used for summary statistics and relevant median plots, whereas for individual participant plots by time, the actual PK sampling time will be used.

For the primary objective, natural log transformed AUC_{inf} (if data permit), otherwise AUC_{last}, and C_{max} for PF-07817883 will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect in Periods 1 to 4. Estimates of the adjusted mean differences (test-reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% confidence intervals for the ratios. Treatment A will be the Reference treatment while Treatments B, C, and D will be the Test treatments.

6.2. Secondary Endpoint(s)

All safety analyses will be performed on the safety population.

6.2.1. Adverse Events

AEs will be listed and summarized by treatment and overall and in accordance with sponsor reporting standards using the safety population defined in Section 4.

Incidence and severity of TEAE tables will additionally be produced ('All causality' and 'Treatment related,' separately) to summarize the total number of adverse events by preferred term, which will be reported by treatment and overall, in accordance with sponsor reporting standards using the safety analysis set defined in Section 4.

The AEs will be presented sorted in descending frequency based on the overall number of AEs (by preferred term or system order class as appropriate) across treatments.

6.2.2. Clinical Safety Laboratory Data

Safety laboratory data will be listed and summarized by treatment and overall, in accordance with the sponsor reporting standards using the safety analysis set defined in Section 4. Baseline is as defined in Section 3.2.2.

Data collected at screening that are used for inclusion/exclusion criteria, will be considered source data, and will not be required to be reported, unless otherwise noted.

In summary and listing tables, laboratory abnormalities occurring pre-dose on Day -1 for each period starting with Period 2, will be attributed to the dose from the previous period (e.g., an occurrence pre-dose at Period 2 Day -1 will be attributed to the Period 1 dose). Unplanned assessment will be excluded from the safety summary but will be listed.

6.2.3. Vital Signs Data

Absolute values and changes from baseline (as defined in Section 3.2.3) in supine systolic and diastolic blood pressure and pulse rate will be listed, and summarized by treatment and

timepoint, according to sponsor reporting standards using the safety population defined in Section 4. Tables will be paged by parameter.

Mean absolute values and mean changes from baseline for systolic and diastolic blood pressure and pulse rate will be plotted against time point. On each plot, there will be 1 line for each treatment with all treatments on the same plot. Corresponding individual participant 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.

Maximum and minimum absolute values and changes from baseline (as defined in Section 3.2.3) for supine vital signs will also be summarized descriptively by treatment using categories as defined in Appendix 2. 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. All values meeting the criteria of potential clinical concern will be listed.

Individual participant profiles will be created for those participants meeting the sponsor abnormality criteria – including absolute values, change from baseline and percent change from baseline.

Values meeting the categorical criteria occurring pre-dose on Day 1 for each period starting with Period 2, will be attributed to the dose from the previous period (e.g., an occurrence pre-dose at Period 2 Day 1 will be attributed to the Period 1 dose).

Data collected at screening that are used for inclusion/exclusion criteria, will be considered source data, and will not be required to be reported, unless otherwise noted. Unplanned assessment will be listed but will be excluded from safety summary except for categorical summaries.

6.2.4. Electrocardiogram Data

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by treatment and timepoint using sponsor reporting standards, using the safety analysis set defined in Section 4. Baseline is as defined in Section 3.2.4. Tables will be paged by parameter.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time post-dose. On each plot there will be one line for each treatment. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Changes from baseline in QTcF will also be plotted separately against drug concentrations of PF-07817883. This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Different symbols will be used for each treatment.

Maximum increase from baseline for QTcF, heart rate, PR and QRS values will be summarized by treatment according to sponsor reporting standards.

ECG endpoints and changes from baseline (QTcF [1], PR and QRS) will also be summarized descriptively by treatment (if applicable) using categories as defined in Appendix 2 . Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned postdose time points will be counted in these categorical summaries. The frequency of uncorrected QT values above 500 ms will also be tabulated.

Individual participant profiles will be created for those participants meeting the sponsor's abnormality criteria – including absolute values, change from baseline and percent change from baseline.

Values meeting the categorical criteria occurring pre-dose on Day 1 for each period starting with Period 2, will be attributed to the treatment from the previous period (e.g., for cohort 1, an occurrence pre-dose at Period 2 Day 1 will be attributed to the Period 1 dose).

Listings of participants with any single post-dose value >500msec will also be produced for QTcF.

Data collected at screening that are used for inclusion/exclusion criteria, will be considered source data, and will not be required to be reported, unless otherwise noted. Unplanned assessments will be listed but will be excluded from safety summary except for categorical summaries.

6.3. Other Safety Summaries and Analyses Endpoint(s)

Not applicable

6.4. Other Endpoint(s) (or, Exploratory Endpoint[s])

6.4.1. Additional Plasma PK Parameters

See Section 6.1

6.4.2. Drug Product Acceptability

For each item in the Drug-Product Acceptability Questionnaire, summary statistics will include number and percent with each numeric score (1,2,3,4,5) and negative (1, 2), neutral (3) and positive (4, 5) scores and will be presented by item and domain (Appearance, Mouthfeel, Taste, Swallowability and Overall assessment),using the safety population defined in Section 4.

6.4.3. Other Analyses

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.

6.5. Subset Analyses

No subset analyses will be performed.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

Demographics data (age, biological sex, race, ethnicity, body weight, body mass index and height) will be summarized across all participants in the safety population (as defined in Section 4), by treatment as described in Section 5.2.1 or Section 5.2.2 (as appropriate).

6.6.2. Study Conduct and Participant Disposition

Participant evaluation groups will show end of study participant disposition by treatment and will show which participants were analyzed for PK, safety and other endpoints, which may not be produced in one table. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment.

6.6.3. Study Treatment Exposure

Not applicable.

6.6.4. Concomitant Medications and Nondrug Treatments

All prior and concomitant medication(s) as well as non-drug treatment(s) will be provided in listings.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1. FDA. Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Updated 24-AUG-2018. Accessed 29-AUG-2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqtc-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-0

Appendix 1. PK Analyses – Example of SAS Code for mixed effects model

An example of the PROC MIXED code:

```
proc mixed data=tab.pk method=reml;
        class seq period trt participant;
        model &var=seq period trt/ residual ddfm=KR;
        random participant(seq);
        lsmeans trt;
        estimate 'B vs A' trt -1 1 0 0 /cl alpha=0.1;
        estimate 'C vs A' trt -1 0 1 0 /cl alpha=0.1;
        estimate 'D vs A' trt -1 0 0 1 /cl alpha=0.1;
run;
```

Appendix 2. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

Degree of Prolongation	Mild (ms)	Moderate (ms)	Severe (ms)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

Categories for PR and QRS

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

Measurements that fulfill these criteria are to be listed in the report.

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	Adverse Event
AUC	Area Under the Curve
$AUC_{extrap\%}$	Percent of AUC_{inf} based on extrapolation
AUC_{inf}	Area Under the Concentration-Time Curve from time zero extrapolated to infinity
AUC_{last}	Area Under the Concentration-Time Curve from time zero to the last measurable concentration
BLQ	Below the Limit of Quantitation
BP	Blood Pressure
CFB	Change from Baseline
C_{last}	Predicted Plasma Concentration at the last quantifiable timepoint
CL	Clearance
CL/F	Apparent Total Body Clearance
C_{max}	Maximum Observed Concentration
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variation
C_{12}	Concentration observed at 12 hours
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
FDA	Food and Drug Administration
H	Hour
HR	Heart rate
ID	Identification
k_{el}	Terminal Phase Rate Constant
LLQ	Lower Limit of Quantitation
ln	Natural log
mg	Milligram
mmHg	Millimeter of mercury
msec	Millisecond
N	Number of participants
N/A	Not Applicable
NC	Not Calculated
ND	Not Done
NS	No Sample
PK	Pharmacokinetic(s)
QTcF	corrected QT (Fridericia method)
rBA	Relative Bioavailability
REML	Restricted Maximum Likelihood
SAP	Statistical Analysis Plan
sec	Second
SoA	Schedule of Activities
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to maximum observed concentration
$t_{½}$	Half life

Abbreviation	Term
V_z/F	Apparent volume of distribution