Protocol C5171001

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, 4-PERIOD, CROSSOVER, FIRST-IN-HUMAN STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE ASCENDING ORAL DOSES OF PF-07293893 ADMINISTERED TO HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan (SAP)

Version: **2**

Date: 21 Mar 2024

Note: Text taken verbatim from the protocol is *italicized* in this document.

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 13 Jul 2023	Final Protocol Amendment 1 07 Jun 2023	N/A	N/A
2 21 Mar 2024	Final Protocol Amendment 1 07 Jun 2023 Protocol Administrative Change Letter (PACL) for Amendment 1 14 Dec 2023	Food effect added to SDD formulation	• Throughout: General updates to add the evaluation of food effect in SDD formulation per PACL 14-Dec-2023. • Section 2.2: tertiary objective of food effect updated to match PACL. Typo of "secondary" corrected. • Section 3.2: footnote of Table 2 updated. • Section 6.2: analysis of food effect in SDD formulation added. • Appendix 3: abbreviation of PACL added.

2. INTRODUCTION

This study will be the first time that *PF-07293893 is administered to humans. The purpose of the study is to evaluate the safety, tolerability, and plasma* pharmacokinetics (*PK*) *of PF-07293893 following administration of escalating single oral doses to healthy adult participants.*

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C5171001. 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.

2.1. Modifications to the Analysis Plan Described in the Protocol

No modification.

2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint
	Primary	*Primary*
Safety Section 6.1	• *To evaluate the safety and tolerability of single ascending doses of PF-07293893 administered orally to healthy adult participants.*	• *Assessment of adverse events, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead electrocardiograms, physical examinations and neurological examinations.*
	Secondary	*Secondary*
PK Section 6.2	• *To evaluate the PK of PF-07293893 following single doses of PF-07293893 administered orally to healthy adult participants.*	• *PK parameters derived from plasma PF-07293893 concentrations:* C_{max}, T_{max}, AUC_{last}, *and if data permit,* AUC_{inf}, *and* $t_{½}$.
	Tertiary/Exploratory	*Tertiary/Exploratory*
PK Section 6.3.1	• *To evaluate additional PK parameters of PF-07293893 following single doses of PF-07293893 administered orally to healthy adult participants.*	• *Additional PK parameters derived from plasma PF-07293893 concentrations:* $C_{max}(dn)$, $AUC_{last}(dn)$ *and if data permit,* $AUC_{inf}(dn)$, *CL/F and* V_z/F .
PK Section 6.3.2	• *To evaluate the PK of PF-07293893 following single dose(s) of a crystalline* and SDD *form of PF-07293893 in fasted and/or fed state, if conducted.*	• *PK parameters derived from plasma PF-07293893 concentrations:* C_{max}, T_{max}, AUC_{last}, *and if data permit,* AUC_{inf}, *and* $t_{½}$.
Biomarker Section 6.3.3	• *To evaluate the effects of single ascending doses of PF-07293893 on biomarker(s) of transporter activity, if feasible & analyzed.*	• *For each biomarker (as applicable):* AUC_{24} *and* C_{max}

There are no estimands for this study.

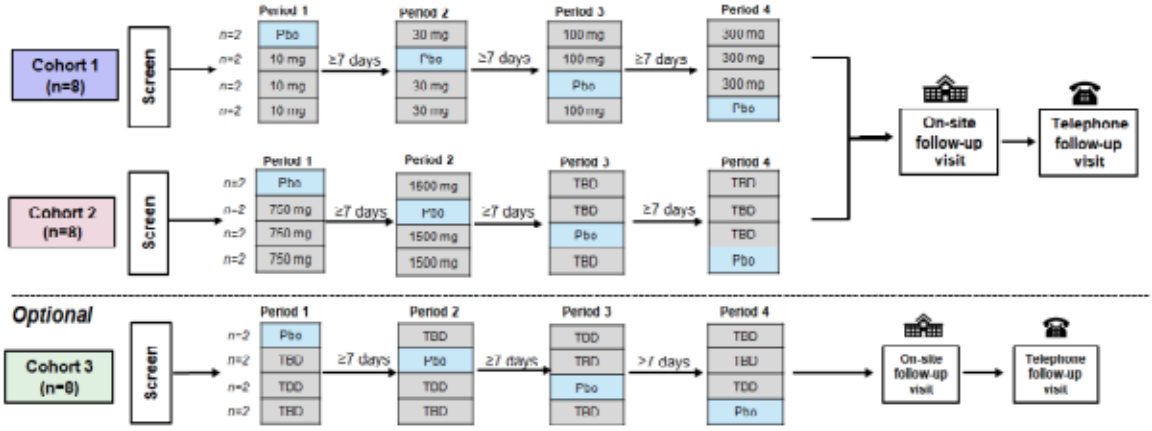
2.3. Study Design

This is a randomized, investigator- and participant-blind, sponsor-open, placebo-controlled, first-in-human, single ascending oral dose, 4-period, crossover study of PF-07293893 administered to healthy adult participants. Approximately 24 healthy adult participants (up to 3 cohorts of approximately 8 participants each) will be enrolled in this study. The first 2 cohorts are planned, and the third cohort is optional. In each period, participants will be randomized to either PF-07293893 or placebo in a ratio of 3:1. Each participant is planned to undergo up to 4 treatment periods receiving up to 4 doses of PF-07293893 and up to 2 doses of placebo.

Precautionary sentinel dosing will be used in any period evaluating escalating doses of PF-07293893 and may be omitted for periods when repeating a dose level or administering a lower dose level than previously evaluated. For periods with sentinel dosing, two participants (1 receiving PF-07293893 and 1 receiving placebo) will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period.

The study design schema is shown below in Figure 1.

Figure 1. Study Design Schema[a,b,c]



a. Doses shown for each cohort except the starting dose in Cohort 1 are planned doses and may be modified based on emerging data from previous cohorts. Similarly, assignment to study intervention may be modified. n represents number of participants.

b. SDD extemporaneous prep will be used for dose escalation in this study. PK for crystalline formulation (fasted/fed) may be studied in remaining periods of Cohort 2 and/or optional Cohort 3 when it becomes available.

c. Precautionary sentinel dosing will be used in any period evaluating escalating doses of PF-07293893. For such periods, 2 participants (1 receiving PF-07293893 and 1 receiving placebo) will be dosed initially before the remaining participants of that period are dosed. Safety and tolerability data through at least 24 hours post-dose for the sentinel participants will be reviewed prior to dosing the remaining participants of that period. Sentinel dosing may be omitted when repeating a dose level or administering a lower dose level than previously evaluated.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Primary endpoints include assessment of adverse events (AEs), clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead electrocardiograms (ECG), physical examinations and neurological examinations during the entire study, by period.

Any events occurring following start of study intervention (ie, treatment with PF-07293893 or placebo) will be counted as treatment emergent.

Events that occur in a non-treatment period (eg, 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 will not be used due to the low number of participants planned to be recruited.

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,
- cardiac monitoring,
- physical examinations,
- neurological examinations.

3.1.1. 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.

3.1.2. Clinical Safety Laboratory Tests

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 last pre-dose measurement in each study period. Change from baseline (CFB) will be calculated for all post-baseline timepoints.

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.

3.1.3. Vital Signs

Single supine blood pressure will be measured at screening, follow-up visit and early termination (ET; if applicable). Triplicate supine measurements will be taken at all other times as specified in the Schedule of Activities (SoA) of the protocol. The average of the triplicate measurements will be calculated prior to analyzing the data. Respiratory rate, pulse rate and temperature will be measured at each timepoint specified 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 in systolic and diastolic BP, pulse rate, temperature, and respiratory rate
- The minimum and maximum post-dose systolic and diastolic BP, pulse rate, temperature, and respiratory rate
- The maximum increase and decrease from baseline over all measurements taken postdose for systolic and diastolic BP, pulse rate, temperature, and respiratory rate values

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

3.1.4. Continuous Cardiac Monitoring

Continuous cardiac monitoring will be performed using telemetry as outlined in the protocol.

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the CRF.

Events deemed of clinical concern will be recorded as AEs and will be summarized as part of the standard AE outputs.

3.1.5. 12-Lead ECG

A single 12-lead ECG will be obtained on all participants at screening, follow-up visit and at ET (if applicable). 12-lead ECGs will be recorded in triplicate at all other times as specified in the the protocol. The average of the triplicate readings collected at each assessment time will be calculated for each ECG parameter. If one or two of the triplicates are missing, the non-missing values will be used for the average, and missing values will not be imputed.

The mean of the three averages *of the triplicate ECG measurements collected at -1.0, -0.5, and 0 hours pre-dose on Day 1 of each period will serve as each participant's* baseline value *for that period.* If one or two of the averages are missing, the non-missing averages will be used for the mean, and missing values will not be imputed.

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:

$QTcF\ (msec) = QT\ (msec) / (RR)^{1/3}$, where RR (sec) = 60/Heart Rate (if RR not provided).

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.

3.1.6. Physical Examinations

Complete physical examinations will be conducted at screening or upon admission for a participant's first period in the study. At all other timepoints, a brief physical exam may be performed for the findings during a previous exam or new/open AEs at the investigators discretion. Height and weight will only be measured at the screening visit.

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted.

Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE will be summarized as part of the standard AE output.

3.1.7. Neurological Examinations

Neurological examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation at the nominal time points

specified in the SoA. The neurological exam will consist of assessment of higher cortical function, the cranial nerves, motor function, deep tendon reflexes, sensory exam, and coordination and gait. Additional neurological examinations that are outside of SoA (eg, to evaluate an AE) may be conducted at the discretion of investigator. All neurological exams should be done to the extent needed to assess the participant for any potential changes in neurological status, as determined by the investigator (or designee). Changes in the timing or addition of timepoints for the neurological examinations may occur based on emerging data.

Any untoward findings identified on neurological examinations, conducted during the active collection period will be captured as AEs or SAEs, if those findings meet the definition of an AE or SAE, and will be summarized as part of the standard AE outputs.

3.2. Secondary Endpoint(s)

Blood samples for PK analysis of PF-07293893 will be taken according to the SoA in the protocol. *The plasma PK parameters for PF-07293893, following oral dose administration, will be derived from the plasma concentration-time profiles using standard noncompartmental methods as detailed* in Table 2, *as data permit*. Table 2 also shows the analysis scale and method for each parameter.

In all cases, *actual PK sampling times will be used in the derivation of PK parameters. If actual PK sampling times are not available, nominal PK sampling times will be used in the derivation of PK parameters.*

The following plasma PK parameters as described in Table 2 will be determined.

Table 2. Plasma PF-07293893 PK Parameters

Parameter	***Definition***	***Method of Determination***	**Analysis Scale**	**PF-07293893**
AUC_{last}	*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	D, A
*AUC_{inf}**	*Area under the plasma concentration-time profile from time 0 extrapolated to infinite time*	*AUC_{last} + (C_{last}*/kel), where C_{last}* is the predicted plasma concentration at the last quantifiable timepoint estimated from the log-linear regression analysis*	ln	D, A

C_{max}	*Maximum plasma concentration*	*Observed directly from data*	ln	D, A
T_{max}	*Time for C_{max}*	*Observed directly from data as time of first occurrence*	R	D
$t_{½}$*	*Terminal elimination half-life*	*$Log_e(2)/kel$, where kel 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

Key: ln=natural-log transformed, R=raw (untransformed),
D=displayed with descriptive statistics,
A=analysed using a statistical model (for evaluating food effect)
*=if data permit

T_{last} will also be provided as a support parameter for AUC_{last}. T_{last} values will only be listed and not summarized.

3.3. Other Endpoint(s)

3.3.1. Additional Plasma PF-07293893 Parameters

Additional plasma PF-07296893 PK parameters, as described in Table 3, will be determined.

Table 3. Additional PF-07293893 PK Parameters

Parameter	***Definition***	***Method of Determination***	**Analysis Scale**	**PF-07293893**
*CL/F**	*Apparent clearance*	*$Dose/AUC_{inf}$*	ln	D
*Vz/F**	*Apparent volume of distribution*	*$Dose/(AUC_{inf} \times kel)$*	ln	D
$AUC_{last}(dn)$	*Dose-normalized AUC_{last}*	*$AUC_{last}/Dose$*	ln	D
*$AUC_{inf}(dn)$**	*Dose-normalized AUC_{inf}*	*$AUC_{inf}/Dose$*	ln	D
$C_{max}(dn)$	*Dose-normalized C_{max}*	*$C_{max}/Dose$*	ln	D

Key: ln=natural-log transformed,
D=displayed with descriptive statistics,
*=if data permit

3.3.2. Plasma PF-07293893 PK parameters during crystalline form period if conducted

The plasma PF-07296893 PK parameters described in Table 2 and dose normalized PK parameters (if required) in Table 3 will also be determined after crystalline PF-07293893 oral suspension administration.

3.3.3. Transporter biomarkers (optional)

Transporter biomarkers (eg, CCI) will be analyzed if feasible and deemed necessary. The AUC_{24} and C_{max} of each transporter biomarker will be derived if applicable, where the analysis scale is ln.

3.4. Baseline Variables

Not applicable.

3.5. Safety Endpoints

See Section 3.1 for details.

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***	**Applicable Analysis** (for additional information refer to section 6)
Enrolled	*"Enrolled" means a participant'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.	
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 study intervention they actually received.*	Section 6.1 Safety endpoints summaries and anlayses

Participant Analysis Set	*Description*	**Applicable Analysis** (for additional information refer to section 6)
PK Concentration Set	*All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and in whom at least 1 plasma concentration value is reported.*	Section 6.2, Section 6.3.1, Section 6.3.2 PK endpoints
PK Parameter Set	*All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and have at least 1 of the PK parameters of interest calculated.*	Section 6.2, Section 6.3.1, Section 6.3.2 PK endpoints
Biomarker Concentration Set	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and in whom at least 1 plasma biomarker concentration value is reported.	Section 6.3.3 Biomarker endpoints
Biomarker Parameter Set	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and have at least 1 of the Biomarker parameters of interest calculated.	Section 6.3.3 Biomarker endpoints

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 dose and treatment. Each formulation of PF-07293893 administered during the study and fasting status will be considered as separate treatments. If a dose level is repeated across 2 or more cohorts, the data will be combined, unless the dose is in a different formulation or food state, in which case the dose would be reported separately.

Unless otherwise stated, the summary tables and/or statistical analyses will only include a single pooled placebo group across all included cohorts with SDD formulation. Placebo will be pooled from all dose escalation periods but not for the fed period (if conducted) nor for cyrstalline formulation period (if conducted).

5.2.1. Analyses for Continuous Endpoints

Unless otherwise stated, continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values.

Geometric mean and geometric cv% will also be presented for continous variables using ln analysis scale.

5.2.2. Analyses for Categorical Endpoints

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

5.2.3. Mixed Effect Model

A mixed effects model with treatment as a fixed effect and participant as a random effect will be used for the analysis of food effect on PF-07296893 PK endpoints.

Estimates of the adjusted (least squares) mean differences (Test-reference) and corresponding 90% confidence intervals (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.

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 SAS code is provided in Appendix 2.

5.3. Methods to Manage Missing Data

5.3.1. Missing Safety Data

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

5.3.2. Missing PK Concentration Data

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 "<LLOQ", where LLOQ will be replaced with the value for the lower limit of quantification (LLOQ).

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

1. A concentration has been collected as ND (ie not done) or NS (ie no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist/statistician.

Note that summary statistics will not be presented at a particular timepoint if more than 50% of the data are missing.

Participants who experience events that may affect their PK profile (e.g., lack of compliance with dosing or vomiting) may be excluded from the PK analysis. At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.3.3. Missing Plasma PK Parameters

Actual PK sampling times will be used in the derivation of plasma PK parameters.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (ie 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. For statistical analyses (i.e. mixed effects model), PK parameters coded as NC will also be set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

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 may not be included in the calculation of summary statistics or statistical analyses.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

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

6.1.1. Adverse Events

Adverse events will be listed and summarized by dose and treatment (if applicable) 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.

6.1.2. Clinical Safety Laboratory Tests

Safety laboratory data will be listed and summarized by dose and treatment (if applicable) and overall, in accordance with the sponsor reporting standards using the safety analysis set defined in Section 4. Baseline is as defined in Section 3.1.2.

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 treatment from the previous period (eg, for Cohort 1, an occurrence pre-dose at Period 2 Day -1 will be attributed to the Period 1 dose).

6.1.3. Vital Signs

Absolute values and CFB in supine systolic and diastolic BP, pulse rate, temperature and respiratory rate will be listed and summarized by dose and treatment and timepoint, according to sponsor reporting standards, using the safety analysis set defined in Section 4. Baseline is as defined in Section 3.1.3.

Mean absolute values and CFB for supine systolic and diastolic BP, pulse rate, temperature, and respiratory rate will be plotted against time point. On each plot there will be one line for each treatment with all treatments on the same plot. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum increase and decrease from baseline over all measurements taken post-dose for supine systolic and diastolic BPs, pulse rate, temperature and respiratory rate will be summarized by treatment, according to sponsor reporting standards.

Minimum and/or maximum absolute values and CFB 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. All values meeting the criteria of potential clinical concern will be listed.

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).

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.

6.1.4. Continuous Cardiac Monitoring

Data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants.

All abnormal rhythms will be recorded and reviewed by the investigator for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the CRF. Events deemed of clinical concern will be recorded as AEs and will be summarized as part of the standard AE outputs.

6.1.5. 12-Lead ECG

Absolute values and CFB in QT, heart rate, QTcF, PR and QRS will be summarized by dose and treatment and timepoint using sponsor reporting standards, using the safety analysis set defined in Section 4. Baseline is as defined in Section 3.1.5.

Mean CFB 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 CFB will also be produced for each treatment.

Changes from baseline in QTcF will also be plotted separately against drug concentrations of PF-07293893. This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Placebo data will also be included (with drug concentration set to zero). Different symbols will be used for each treatment.

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

ECG endpoints and CFB (QTcF, PR and QRS) will also be summarized descriptively by dose and treatment using categories as defined in Appendix 1. 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.

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 >500 msec 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.

6.1.6. Physical Examinations

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE will be recorded as AEs or SAEs and will be summarized as part of the standard AE outputs.

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.

6.1.7. Neurological Examinations

Neurological examination data collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward neurological examination findings that are identified during the active collection period and meet the definition of an AE or SAE will be recorded as AEs or SAEs and will be summarized as part of the standard AE outputs.

6.2. Secondary Endpoint(s)

The PK parameters detailed in Section 3.2 will be listed and summarized for participants in the PK Parameter Analysis Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.2 and 5.3.3. Each PK parameter will be summarized by dose (and formulation and fasting condition, if appropriate) as applicable. Each summary will include the set of summary statistics as specified in Table 4.

Table 4. Summary Statistics for PF-07293893 Plasma PK Parameters

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}*, C_{max},	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum
$t_{1/2}$*	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

*If data permit

Supporting data from the estimation of t½ 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.

PF-07293893 concentrations will be presented using participants in the PK Concentration Set (as defined in Section 4) and will include:

- a listing of all concentrations sorted by participant ID, dose and treatment (if applicable) 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 treatment (if applicable) 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) and treatment (if applicable) against actual time post-dose (there will be separate spaghetti plots for each dose and treatment [if applicable] 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 and treatment [if applicable] 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) and treatment (if applicable).
- 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) and treatment (if applicable).

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-07293893 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.

To assess any food effect in SDD formulation as a tertiary objective, a mixed effects model will be performed separately on the natural log transformed AUC_{inf}, AUC_{last}, and C_{max} with fasting condition included as a fixed effect and participant as a random effect as described in Section 5.2.3. Only data from the respective periods in the cohort 3 will be included. The fasted state will be the reference and the fed state will be the test treatment.

6.3. Other Endpoints

6.3.1. Additional Plasma PF-07293893 Parameters

Additional PK parameters detailed in Section 3.3.1 will be listed and summarized for participants in the PK Parameter Analysis Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.2 and 5.3.3. Each PK parameter will be summarized by dose (and formulation and fasting condition, if appropriate) as applicable. Each summary will include the set of summary statistics as specified in Table 5.

Table 5. Summary Statistics for Additional PF-07293893 Plasma PK Parameters

Parameter	Summary Statistics
CL/F*, V_z/F*, AUC_{last}(dn), AUC_{inf} (dn)*, C_{max} (dn)	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

*If data permit

Box and whisker plots for dose-normalized PK parameters [AUC_{inf} (dn), AUC_{last} (dn) and C_{max}(dn)] will be presented in logarithmic scale by dose and treatment (if applicable) and overlaid with observed values of individual participants and geometric means. Geometric means will have a different symbol than the individual values. Individual values from different cohorts will also have a different symbol. A footnote will be added to the plots to indicate that geometric means are presented and that data from all cohorts are presented on the plot.

The nominal PK sampling time will be used for summary statistics and relevant plots.

6.3.2. Plasma PF-07293893 PK parameters during crystalline form period if conducted

If the formulation and/or food effects are assessed, the PK parameters described in Section 3.3.2 will also be summarized descriptively as described above in Section 6.2 by formulation and/or fasting condition.

To assess any food effect in crystalline formulation, a mixed effects model *will be performed separately on the natural log transformed AUC_{inf}, AUC_{last}, and C_{max} (dose-normalized prior to analysis, if appropriate)* with fasting condition *included as a fixed effect and participant as a random effect* as described in Section 5.2.3. If performed, only data from the respective periods that includes the crystalline formulation will be included. The fasted state will be the reference and the fed state will be the test treatment.

6.3.3. Transporter biomarkers (optional)

If analyzed, the AUC_{24} and C_{max} of transporter biomarkers (eg, [redacted]) will be listed and summarized for participants in the Biomarker Parameter Analysis Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.2. Each biomarker parameter will be summarized by dose (and formulation and fasting condition, if appropriate) as applicable. Each summary will include N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

If analyzed, biomarker concentrations will be presented using participants in the Biomarker Concentration Set (as defined in Section 4) and will include listing, summary statistics, and plots similarly described in Section 6.2.

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 biomarker concentration is quantifiable in the matrix.

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

6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

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

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition by dose and treatment (if applicable) and overall and will show which participants were analyzed for PK and safety. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the sponsor reporting standards.

6.5.3. Study Treatment Exposure

Not applicable.

6.5.4. Concomitant Medications and Nondrug Treatments

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

6.5.5. Specified Genetics

Genotyping or pharmacogenomic data from specified genetics 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.

6.5.6. Other Exploratory Biomarkers

Circulatory biomarker data from specified protein 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.

6.6. Safety Summaries and Analyses

See Section 6.1.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study.

However, preliminary draft safety and PK data will be reviewed after each study period. This is a sponsor-open study, with the investigator and participant blinded to study treatment. A limited number of Pfizer personnel (eg, PK assay specialist, medical monitor, clinical lead, study clinician, statistician, clinical programmer, and clinical pharmacology lead) will be unblinded to treatments in order to permit real-time interpretation of the safety and pharmacokinetic data, and to provide information necessary for dose escalation decisions and

to potentially alter the dose escalation sequence. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer personnel and will not be released to the investigator/study staff until the conclusion of the study. Unblinding will not be performed until the final database has been locked for all cohorts. Final analysis will follow the official database release.

7.2. Interim Analyses and Summaries

Not applicable.

APPENDICES

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

Categories for QTcF

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 (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 (mmHg)	min. <90	
Systolic BP (mmHg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mmHg)	min. <50	
Diastolic BP (mmHg) 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 2. Example SAS Code for Statistical Analyses

```
proc mixed data = dataset;
        class subjid trt;
        model &var = trt /residual ddfm = kr;
        random subjid;
        lsmeans trt / diff cl alpha = 0.1;
run;
```

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	Adverse event
AUC	Area under the curve
AUC_{24}	Area under the curve from time zero to 24 hours
$AUC_{extrap\%}$	Percent of AUC_{inf} based on extrapolation
AUC_{inf}	Area Under the Concentration-Time Curve from time zero extrapolated to infinity
AUC_{inf} (dn)	Dose normalized 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
AUC_{last} (dn)	Dose normalized area Under the Concentration-Time Curve from time zero to the last measurable concentration
BLQ	Below the limit of quantitation
BP	Blood pressure
bpm	Beats per minute
CFB	Change from Baseline
CI	Confidence interval
CL	Clearance
C_{last}	Last quantifiable concentration
CL/F	Apparent total body clearance
C_{max}	Maximum observed concentration
C_{max} (dn)	Dose normalized maximum observed concentration
CCI [redacted]	
CRF	Case report form
CSR	Clinical study report
CV	Coefficient of Variation
ECG	Electrocardiogram
ET	Early termination
CCI [redacted]	
ID	Identification
k_{el}	Elimination rate constant
LLOQ	Lower limit of quantitation
ln	Natural log
max	Maximum
min	Minimum
mmHg	Millimeter of mercury
msec	Millisecond
N	Number of participants
N/A	not applicable
NC	Not Calculated
ND	Not Done

Abbreviation	Term
NS	No Sample
PACL	Protocol Administrative Change Letter
PK	Pharmacokinetic(s)
QTc	Corrected QT
QTcF	Corrected QT (Fridericia method)
REML	Restricted maximum likelihood
SAE	Serious adverse events
SAP	Statistical analysis plan
SDD	Spray dried dispersion
sec	Second
SoA	Schedule of Activities
TEAE	Treatment-Emergent Adverse Event
T_{last}	Time of last measurable concentration
T_{max}	Time to maximum observed concentration
t½	Half life
Vz/F	Apparent volume of distribution