Protocol C5161001

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, CROSSOVER, FIRST-IN-HUMAN STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE ASCENDING ORAL DOSES OF PF-07853578 ADMINISTERED TO HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan
(SAP)

Version: **1**

Date: 23 Jun 2023

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NOTE: Italicized text within this document has been taken verbatim from the protocol.

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 23-Jun-2023	Final Protocol Amendment 1, 06 June 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 C5161001. 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
	Primary:	***Primary:***
Safety Section 6.1	*To evaluate the safety and tolerability of single ascending doses of PF-07853578 administered orally to healthy adult participants.*	*Assessment of AEs, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead ECGs, PEs, and neurological examinations.*
	Secondary:	***Secondary:***
PK Section 6.2	*To evaluate the PK of PF-07853578 following single doses of PF-07853578 administered orally to healthy adult participants.*	*PK parameters derived from plasma PF-07853578 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-07853578 following single doses of PF-07853578 administered orally to healthy adult participants.*	*Additional PK parameters derived from plasma PF-07853578 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 effect of food on the PK of PF-07853578 following single doses of PF-07853578 administered orally to healthy adult participants (if conducted).*	*PK parameters derived from plasma PF-07853578 concentrations after a high-fat/high-calorie meal: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf} and $t_{½}$.*
PK Section 6.3.3	*To evaluate the PK of PF-07853578 following single oral doses of an IDS oral solution of PF-07853578 administered orally to healthy adult participants (if conducted).*	*PK parameters derived from plasma PF-07853578 concentrations after IDS oral solution dosing: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf} and $t_{½}$.*

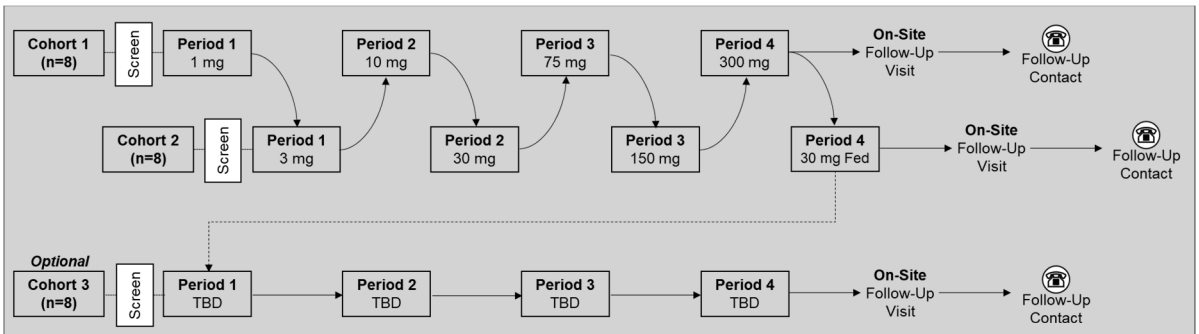
There are no estimands for this study.

2.3. Study Design

This study is a randomized, investigator- and participant-blind, sponsor-open, placebo-controlled, FIH, single ascending dose, 4-period, crossover, interleaving design study of PF-07853578 orally 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 optional third cohort will only be used if the objectives of the study are not fulfilled in Cohort 1 and Cohort 2. Each participant is planned to undergo 4 treatment periods receiving up to 4 doses of PF-07853578 and up to 2 doses of placebo. In each period, participants will be randomized to either PF-07853578 or placebo in a ratio of 6:2. A diagram of the study design is shown in Figure 1.

Precautionary sentinel dosing will be used in any period evaluating escalating doses of PF-07853578. Two participants (1 receiving PF-07853578 and 1 receiving placebo) within a period 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.

Figure 1. Study Design: Interleaving, Placebo-Controlled, 4-Period, Crossover Design



- Each period will consist of admission on Day -1, dosing on Day 1, and discharge at approximately 72 hours post-dose. Within a participant, there will be a washout interval of ≥10 days between doses.
- In each period, 6 participants will be randomized to receive PF-07853578, and 2 participants will be randomized to receive matching placebo.
- Precautionary sentinel dosing will be employed. Two participants (1 receiving PF-07853578 and 1 receiving placebo) within a period 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.
- The starting dose level in Period 1 of Cohort 1 is 1 mg. All other planned dose levels in other periods and cohorts may be adjusted pending emerging safety, tolerability, and PK data from previous periods and cohorts.
- Optional exploratory assessments: 1) effect of food on PF-07853578 PK and/or 2) evaluation of PK of an intermediate dosage strength oral solution of PF-07853578.
- Dose escalation to occur following review of PK data through at least 24 hours post-dose and safety and tolerability data through at least 48 hours post-dose of the current period. Cumulative safety and tolerability from all previous periods will also be reviewed.
- On-site follow-up visit to occur on 7-10 days after administration of the final dose of study intervention. Follow-up contact may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.

Screening activities will be completed over the 28 days prior to randomization in Period 1. In each period, participants will be admitted to the CRU on Day -1 and will remain in the CRU through at least the 72-hour assessments on Day 4. Participants may remain in the CRU after completion of Day 4 activities at the discretion of the investigator or if safety, tolerability, or PK data dictate the need to prolong confinement in the CRU. Participants will

receive a single oral dose of PF-07853578 or placebo on Day 1 of each period. Dose levels will be escalated to bracket the expected clinical dose range, but the projected exposures will not exceed the predefined human exposure limits. Within an individual participant, there will be a washout interval of at least 10 days between doses. The total duration of participation from the screening visit to the telephone follow-up contact will be approximately 17 weeks for each participant. Participants will return for an on-site follow-up visit 7-10 days after the final dose of study intervention. The follow-up contact may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.

Dosing will occur in the fasted state for all periods, except if an optional exploratory assessment of the effect of food on PF-07853578 PK is conducted. If the food effect is evaluated, it is anticipated that study intervention will be administered in the fed state in the last period of Cohort 2 or Cohort 3 at a dose level that was previously administered fasted within the same cohort. However, study intervention may be administered in the fed state during any of the study periods/cohorts if thought necessary to achieve study objectives. The actual dose level will be selected based on emerging safety, tolerability, and PK data but will be expected to achieve approximate projected therapeutic exposures.

If evaluated, the IDS oral solution of PF-07853578 is anticipated to be assessed in the last period of Cohort 2 or Cohort 3 at a dose level that was previously administered as a suspension within the same cohort. However, the IDS oral solution may be administered during any of the study periods/cohorts if thought necessary to achieve study objectives.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Primary endpoints include assessment of adverse events (AEs) and treatment-emergent adverse events (TEAEs), clinical safety laboratory abnormalities, vital signs, ECG parameters, cardiac monitoring, and physical and neurological examinations during the entire study, by period.

Any events occurring following start of study intervention (ie, treatment with PF-07853578 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 (AEs) 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 AE is considered a 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. 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 last pre-dose measurement in each study period.

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

The maximum decrease and increase from baseline over all measurements taken post-dose will be calculated for supine systolic and diastolic blood pressures and pulse rates. 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.

3.1.4. Electrocardiograms

A single 12-lead ECG will be obtained on all participants at screening, follow-up visit and at early termination (if applicable). 12-lead ECGs will be recorded in triplicate at all other times as detailed in the SoA in the protocol. The average of the triplicate readings collected at each assessment time will be calculated for each ECG parameter.

The average of the triplicate ECG measurements over the 3 pre-dose measurement times (-1H, -0.5H, and pre-dose 0H; total of 9 ECG measurements) collected before morning dose administration on Day 1 will serve as each participant's baseline value in each study period.

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:

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

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.

3.1.5. 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.

3.1.6. 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 neurological examination findings that are identified 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.

3.1.7. 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 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-07853578 will be taken according to the SoA in the protocol.

The plasma PK parameters for PF-07853578*, 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 shows the analysis scale and method for each parameter.

In all cases, a*ctual 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. Summary of PF-07853578 plasma PK parameters to be calculated.

Parameter	Analysis Scale	PF-07853578
AUC_{inf}*	ln	A, D
AUC_{last}	ln	A, D
C_{max}	ln	A, D
T_{max}	R	D
$t_{½}$*	R	D

- *=if data permits. Abbreviations: A=analyzed using a statistical model (if applicable); D=displayed with descriptive statistics as outlined in Table 4 in Section 6.2; ln=natural-log transformed; R = raw (untransformed).

3.3. Other Endpoint(s)

3.3.1. Additional Plasma PF-07853578 PK Parameters

Additional plasma PF-07853578 PK parameters, as described in Table 3, will be determined:

Table 3. Additional PF-07853578 Plasma PK Parameters

Parameter	Analysis Scale	PF-07853578
AUC_{inf} (dn)*	ln	D
AUC_{last} (dn)	ln	D
C_{max} (dn)	ln	D
CL/F*	ln	D
V_z/F*	ln	D

*=if data permits. Abbreviations: D=displayed with descriptive statistics as outlined in Table **5** in Section 6.3.1 ; dn = normalized to a 1 mg PF-07853578 dose; ln=natural-log transformed; R = raw (untransformed).

3.3.2. Plasma PF-07853578 PK Parameters During Food Effect Period (if conducted)

The plasma PF-07853578 PK parameters described in Table 2 and Table 3 will also be determined during the fed period.

3.3.3. Plasma PF-07853578 PK Parameters During IDS Oral Solution Period (if conducted)

The plasma PF-07853578 PK parameters described in Table 2 and Table 3 will also be determined after IDS oral solution administration.

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, 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.	
Evaluable	All participants 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 study intervention they actually received.*	Section 6.1 Safety Summaries and Analyses
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, Section 6.3.3 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, Section 6.3.3 PK 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 as applicable. Each formulation of PF-07853578 administered during the study and fasting status will be considered as separate treatments.

Unless otherwise stated the summary tables and/or statistical analyses will only include a single pooled placebo group across all included cohorts. Placebo will be pooled from all dose escalation periods but not for the fed period (if conducted) and for IDS oral solution 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.

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 analysis of the:

- Effect of food on PF-07853578 PK
- PF-07853578 PK of IDS oral solution relative to the oral suspension formulation.

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.

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.

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 LLOQ.

In PK summary tables and plots of 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 time point 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.

5.3.1. Plasma Pharmacokinetic 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 (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 treatment group/analyte 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 plasma 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

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

6.1. Primary Endpoint(s)

6.1.1. Adverse Events

AEs will be summarized by dose and treatment (if applicable) 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 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. Laboratory Data

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 population defined in Section 4 .

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 changes from baseline (as defined in Section 4) in supine systolic and diastolic blood pressure, respiratory rate, and pulse rate will be listed, and summarized by dose and treatment (if applicable) and time point, according to sponsor reporting standards using the safety population defined in Section 4.

Mean absolute values and mean changes from baseline for systolic and diastolic blood pressure, respiratory rate, 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 plots of changes from baseline will also be produced for each treatment.

Maximum and minimum absolute values and changes from baseline (as defined in Section 3.1) for supine vital signs will also be summarized descriptively by dose and 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 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. Electrocardiograms

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by dose and treatment (if applicable) and timepoint using sponsor reporting standards, using the safety analysis set defined in Section 4. Baseline is as defined in Section 3.1.4 .

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-07853578. 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 (if applicable) according to sponsor reporting standards.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by dose and 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.

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.

6.1.5. Continuous Cardiac Monitoring

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

6.1.6. Neurological Examinations

Neurological examinations will be performed as outlined in the protocol. Data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants.

All abnormality will be recorded and reviewed by the investigator for the presence of neurological examination findings 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.

6.1.7. Physical Examination

Physical examinations will be performed as described in the protocol.

Medical history and physical examination 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 examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE, 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.

6.2. Secondary Endpoints

Plasma PK parameters for PF-07853578, as described in Section 3.2, will be listed and summarized descriptively 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 dose (and formulation and fasting condition, if appropriate) as applicable.

Table 4. Summary Statistics for PF-07853578 Plasma PK Parameters

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

$t_{½}$.*	N, arithmetic mean, standard deviation, median, minimum, maximum.

*: if data permit

Supporting data from the estimation of AUC_{inf} will be listed by dose and treatment (if 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}. This data may be included in the clinical study report.

The following plots will be presented using the PK Parameter Set (as defined in Section 4):

– 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 following will additionally 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 for each dose and treatment (if applicable) separately. 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 each nominal time post-dose (produced separately for each dose and treatment (if applicable)), 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.
- median concentration time plots (on both linear and semi-log scales) against nominal time post-dose by dose and treatment (if applicable). One plot for each scale will be presented, which will include all doses and treatments in the same plot.
- 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 and treatment (if applicable), 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.

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.

6.3. Other Endpoints

6.3.1. Additional Plasma PF-07853578 PK Parameters

Additional plasma PK parameters for PF-07853578, as described in Section 3.3.1, will be listed and summarized descriptively as described in **Table 5** 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 dose (and formulation and fasting condition, if appropriate) as applicable as required in the table below:

Table 5. Summary statistics to be produced for additional plasma PK Parameters for PF-07853578

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

*: if Data Permit

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.

6.3.2. Plasma PF-07853578 PK Parameters During Food Effect Period (if conducted)

Plasma PK parameters for PF-07853578 on Fed State as described in Section 3.3.2 will be listed and summarized descriptively as described in Section 6.2 for participants in the PK Parameter Set as defined in Section 4.

Natural log_e transformed AUC_{inf} (as data permit), AUC_{last}, and C_{max} (dose-normalized prior to analysis, if appropriate) of PF-07853578 on fasted state or on fed state will be analyzed using a mixed effect model as described in Section 5.2.3, using only data from the respective periods that includes the two treatments of interest. The test treatment will be PF-07853578 administered with food in comparison to the reference treatment of PF-07853578 administered on fasted state.

6.3.3. Plasma PF-07853578 PK Parameters During IDS Oral Solution Period (if conducted)

Plasma PK parameters for PF-07853578 as described in Section 3.3.3 will be listed and summarized descriptively as described in Section 6.2 for participants in the PK Parameter Set as defined in Section 4. .

Natural log_e transformed AUC_{inf} (as data permit), AUC_{last} , and C_{max} (dose-normalized prior to analysis, if appropriate) of PF-07853578 administered as a suspension or administered as IDS oral solution will be analyzed using a mixed effect model as described in Section 5.2.3,

using only data from the respective periods that includes the two treatments of interest. The test treatment will be PF-07853578 administered as IDS oral solution in comparison to the reference treatment of PF-07853578 administered as a suspension.

6.3.4. Banked Biospecimens

Banked biospecimens will be collected and retained for future analyses but will not be analysed specifically for this study and will not be included in the CSR.

6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

6.5.1. 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) 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 end of study participant disposition by dose and/or treatment when applicable and overall and will show which participants were analyzed for PK and safety, which may not be produced in one table. Frequency counts and percentages will be supplied for participant discontinuation(s) by dose and/or treatment when applicable.

6.5.3. Study Treatment Exposure

Not applicable.

6.5.4. Concomitant Medications and Non-drug Treatments

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

6.6. Safety Summaries and Analyses

See Section 6.1.

7. INTERIM ANALYSES

7.1. Introduction

No 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. PK Analyses – Example of SAS Code for mixed effects model

An example of the PROC MIXED code:

```
proc mixed data=tab.pk;
        class trt subject;
        model &var = trt / ddfm=KR;
        random subject /subject=subject;
        lsmeans trt/ diff cl alpha=0.1;
run;
```

Appendix 2. 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 (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_{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
CFB	Change from Baseline
CL	Clearance
CL/F	Apparent total body clearance
C_{max}	Maximum observed concentration
C_{max} (dn)	Dose normalized maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of Variation
ECG	Electrocardiogram
FIH	First in human
H	Hour
HR	Heart rate
ID	Identification
IDS	Intermediate dosage strength
LLOQ	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
PE	Physical examination
PK	Pharmacokinetic(s)
QTc	corrected QT
QTcF	corrected QT (Fridericia method)

Abbreviation	Term
REML	restricted maximum likelihood
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to maximum observed concentration
$t_{½}$	Half life
V_z/F	Apparent volume of distribution