Protocol C4001001

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, CROSSOVER, FIRST-IN-HUMAN STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE ASCENDING ORAL DOSES OF PF-06954522 IN HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan
(SAP)

Version: **1**

Date: **14 Sept 2023**

TABLE OF CONTENTS

LIST OF TABLES 4
LIST OF FIGURES 4
APPENDICES 4
1. VERSION HISTORY 5
2. INTRODUCTION 5
2.1. Modifications to the Analysis Plan Described in the Protocol 5
2.2. Study Objectives, Endpoints, and Estimands 5
2.3. Study Design 6
3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS 7
3.1. Primary Endpoint(s) 7
3.1.1. Adverse Events 8
3.1.2. Clinical Safety Laboratory Data 8
3.1.3. Vital Signs 8
3.1.4. Continuous Cardiac Monitoring 9
3.1.5. Electrocardiograms 9
3.1.6. Physical Examinations 10
3.2. Secondary Endpoint(s) 10
3.3. Other Endpoint(s) 11
3.3.1. Additional Plasma PF-06954522 PK Parameters 11
3.3.2. Plasma PF-06954522 PK Parameters During Food Effect Period (if conducted) 12
CCI [redacted] 12
3.3.4. Safety Summaries and PK Parameters During Japanese Cohort (if conducted) 12
3.4. Baseline Variables 12
3.5. Safety Endpoints 12
4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS) 13
5. GENERAL METHODOLOGY AND CONVENTIONS 14
5.1. Hypotheses and Decision Rules 14
5.2. General Methods 14
5.2.1. Analyses for Continuous Endpoints 14

5.2.2. Analyses for Categorical Endpoints....14
5.2.3. Mixed Effects Model....14
5.3. Methods to Manage Missing Data....15
5.3.1. Concentrations Below the Limit of Quantification....15
5.3.2. Deviations, Missing Concentrations and Anomalous Values....15
5.3.3. Plasma Pharmacokinetic Parameters....16
6. ANALYSES AND SUMMARIES....16
6.1. Primary Endpoint(s)....16
6.1.1. Adverse Events....16
6.1.2. Clinical Safety Laboratory Data....17
6.1.3. Vital Signs....17
6.1.4. Continuous Cardiac Monitoring....18
6.1.5. Electrocardiograms....18
6.1.6. Physical Examinations....19
6.2. Secondary Endpoint(s)....19
6.3. Other Endpoint(s)....20
6.3.1. Additional Plasma PF-06954522 PK Parameters....20
6.3.2. Plasma PF-06954522 PK Parameters During Food Effect Period (if conducted)....21
CCI [redacted] 21
6.3.4. Safety Summaries and PK Parameters During Japanese Cohort (if conducted)....22
6.3.5. Banked Biospecimens....22
6.4. Subset Analyses....22
6.5. Baseline and Other Summaries and Analyses....22
6.5.1. Baseline Summaries....22
6.5.2. Study Conduct and Participant Disposition....22
6.5.3. Study Treatment Exposure....22
6.5.4. Concomitant Medications and Nondrug Treatments....23
6.6. Safety Summaries and Analyses....23
7. INTERIM ANALYSES....23
7.1. Introduction....23
7.2. Interim Analyses and Summaries....23

8. REFERENCES 23
APPENDICES 24

LIST OF TABLES

Table 1. Summary of Changes 5
Table 2. Summary of PF-06954522 plasma PK parameters to be calculated 11
Table 3. Additional PF-06954522 Plasma PK Parameters 12
CCI [redacted] 12
Table 5. Summary Statistics for PF-06954522 Plasma PK Parameters 19
Table 6. Summary statistics to be produced for additional plasma PK Parameters for PF-06954522 21
CCI [redacted] 21

LIST OF FIGURES

Figure 1. Study Design Schematic: Sequential, Placebo-Controlled, 5-Period, Crossover Design 7

APPENDICES

Appendix 1. PK Analyses – Example of SAS Code for mixed effects model 24
Appendix 2. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern 25
Appendix 3. List of Abbreviations 26

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 14 Sept 2023	Original 17 July 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 C4001001. 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:			
Safety (Section 3.1)	*To evaluate the safety and tolerability of single oral doses of PF-06954522, administered to healthy adult participants.*	*Assessment of AEs, safety laboratory tests, vital signs (blood pressure, pulse rate,* respiratory rate and *temperature), cardiac telemetry and standard 12-lead ECGs, and PE.*	N/A
Secondary:			
PK (Section 3.2)	*To characterize plasma PK of PF-06954522 following single oral doses of PF-06954522 administered to healthy adult participants.*	*PF-06954522 PK parameters:* AUC_{last}, C_{max}, T_{max}, *and if data permit,* AUC_{inf} *and* $t_{½}$.	N/A
Tertiary/Exploratory:			
PK (Section 3.3.1)	*To further characterize plasma PK of PF-06954522 following single oral doses of PF-06954522 administered to healthy adult participants.*	*Additional PF-06954522 PK parameters:* $AUC_{last}(dn)$, $C_{max}(dn)$, *and if data permit,* $AUC_{inf}(dn)$, *CL/F, and* V_z/F.	N/A
PK (Section 3.3.2)	*Optional: to characterize the effect of food (high-fat breakfast) on the plasma PK of PF-06954522*	*PF-06954522 PK parameters after a high-fat meal:* AUC_{last}, C_{max}, T_{max}	N/A

	following single oral doses of PF-06954522 in healthy adult participants.	*and if data permit, AUC_{inf}, CL/F, V_z/F and $t_{½}$.*	
CCI			N/A
Safety and PK (Section 3.3.4)	*Optional: to explore the safety, tolerability, and plasma PK of PF-06954522 in healthy adult Japanese participants.*	*Assessment of AEs, safety laboratory tests, vital signs (blood pressure, pulse rate and temperature), standard 12-lead ECGs and the following PF-06954522 PK parameters in Japanese participants: AUC_{last}, C_{max}, T_{max}, and if data permit, AUC_{inf}, CL/F, V_z/F and $t_{½}$.*	N/A

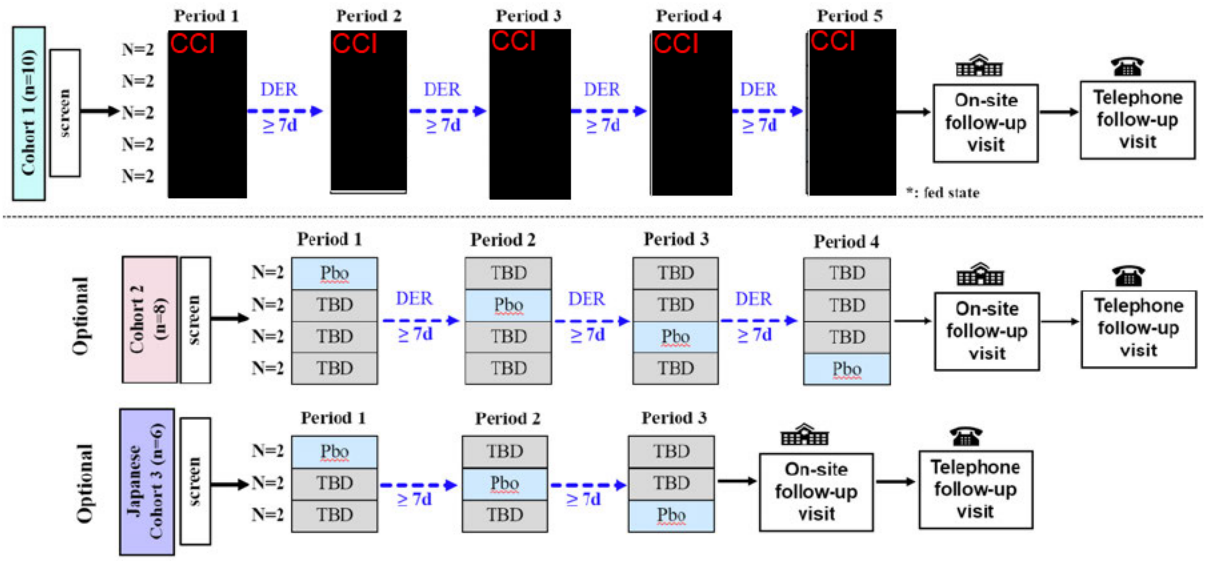
2.3. Study Design

This study is a randomized double-blinded (investigator- and participant-blinded), sponsor-open, first in human (FIH), single-ascending oral dose, 5-period crossover, placebo substitution design in 1 cohort of healthy adult participants. An additional optional cohort, enrolling healthy adult participants in up to 4 crossover periods, may be included to permit assessment of any of the following: repeat of a previously administered dose level; studying additional dose levels as dictated by the evaluated safety, tolerability or PK of earlier dose levels; or any other assessment needed to meet the objectives of this study. A second optional cohort enrolling Japanese participants to receive PF-06954522 or placebo in up to 3 periods, may be included.

Approximately 24 healthy adult participants will be enrolled in the study. This includes up to approximately 10 healthy participants for Cohort 1, up to approximately 8 healthy participants for optional Cohort 2 and up to approximately 6 healthy Japanese participants for the optional Cohort 3. The actual number of Japanese participants may be adjusted based on emerging data or operational factors with a maximum sample size of up to 8 participants (6 receiving PF-06954522 and 2 receiving placebo in each period).

A sample study design schematic is presented in Figure 1. It should be noted that this is for illustrative purposes, only.

Figure 1. Study Design Schematic: Sequential, Placebo-Controlled, 5-Period, Crossover Design



- *All doses in the schematic above (other than the starting dose of C mg) are **for illustrative purposes only**, as treatment sequences, actual doses and dose increments may be adjusted during the study based on emerging safety, tolerability and PK data.*
- *Each period will consist of admission on Day -1, dosing on Day 1, and discharge on Day 4. There will be a washout interval of at least 7 days between consecutive doses administered to an individual participant. The washout interval may be adjusted based on data emerging from previous cohorts/periods.*
- *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 data from all previous periods will also be reviewed.*
- *It is anticipated that the effect of food (dose administration with a high fat breakfast) on PF-06954522 PK will be assessed in the last Period of Cohort 1. This will be assessed at a dose level (to be chosen based on emerging data) that has been previously administered fasted within the same cohort. However, the effect of food may be assessed during any of the study periods/cohorts if thought necessary to achieve study objectives.*
- *On-site follow-up visit to occur 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.*
- *DER: dose escalation review; Pbo: placebo; TBD: to be determined.*

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, cardiac telemetry, ECG parameters, and physical examinations during the entire study by dose, population and dietary allocation.

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.

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 AEs will not be used due to the low number of participants planned to be recruited.

3.1.2. 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 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 and temperature will be measured at each timepoint specified in the protocol.

Baseline for these measures will be defined as the average of the triplicates (if applicable) at last nominal pre-dose measurement time in each study period.

The following endpoints will be determined:

- Change from baseline (CFB) in systolic and diastolic BP, pulse rate, respiratory rate and temperature.
- The minimum and maximum post-dose systolic and diastolic BP, pulse rate, respiratory rate and temperature.

- The maximum increase and decrease from baseline over all measurements taken post-dose for systolic and diastolic BP, pulse rate, respiratory rate and temperature 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. 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. 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. 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. 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.

If any of the 3 individual ECG tracings has a QTcF value >500 msec*, but the mean of the triplicates is not >500* msec*, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-* msec *value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500* msec *will not be included in the categorical analysis unless the average from the triplicate measurements is also >500* msec.

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 [1]:

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

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.

3.1.6. 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 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-06954522 will be taken according to the SoA in the protocol.

The plasma PK parameters for PF-06954522, 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, 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. Summary of PF-06954522 plasma PK parameters to be calculated.

Parameter	Definition	Method of Determination	Analysis Scale	Analysis Method
AUC_{inf}*	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last}* is the predicted plasma concentration at the last quantifiable timepoint estimated from the log-linear regression analysis	ln	A, D
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	A, D
C_{max}	Maximum plasma concentration	Observed directly from data	ln	A, D
T_{max}	Time for Cmax	Observed directly from data as time of first occurrence	R	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

*=if data permits.
Abbreviations: A=analyzed using a statistical model (if applicable); D=displayed with descriptive statistics as outlined in Table 5 in Section 6.2; ln=natural-log transformed; R = raw (untransformed).

3.3. Other Endpoint(s)

3.3.1. Additional Plasma PF-06954522 PK Parameters

Additional plasma PF-06954522 PK parameters, as described in Table 3, will be determined:

Table 3. Additional PF-06954522 Plasma PK Parameters

Parameter	Definition	Method of Determination	Analysis Scale	Analysis Method
AUC_{inf} (dn)*	Dose-normalized AUC_{inf}	AUC_{inf}/Dose	ln	D
AUC_{last} (dn)	Dose-normalized AUC_{last}	AUC_{last}/Dose	ln	D
C_{max} (dn)	Dose-normalized C_{max}	C_{max}/Dose	ln	D
CL/F*	Apparent clearance	Dose/AUC_{inf}	ln	D
V_z/F*	Apparent volume of distribution	Dose/(AUC_{inf} x k_{el})	ln	D

*=if data permits.
Abbreviations: D=displayed with descriptive statistics as outlined in Table 6 in Section 6.3.1; dn = normalized to a 1 mg PF-06954522 dose; ln=natural-log transformed; R = raw (untransformed).

3.3.2. Plasma PF-06954522 PK Parameters During Food Effect Period (if conducted)

If conducted, the plasma PF-06954522 PK parameters described in Table 2 and Table 3 will also be determined during the fed period.

CCI

[redacted]

3.3.4. Safety Summaries and PK Parameters During Japanese Cohort (if conducted)

If conducted, the safety summaries as described in Section 3.1 and the PK parameters as described in Sections 3.2 and 3.3.1 will also be determined for the Japanese cohort.

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.

Population	Description	Applicable Analysis (for additional information refer to section 6)
Enrolled	*"Enrolled" means a participant's, or their legally authorized representatives, 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. Participants will be analyzed according to the product they actually received.*	Section 6.1 Primary Endpoint(s), Section 6.3.4 Safety Summaries and PK Parameters During Japanese Cohort, 6.5.1 Baseline Summaries
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*/urine *concentration value is reported.*	Section 6.2 Secondary Endpoint(s), 6.3.4 Safety Summaries and PK Parameters During Japanese Cohort
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 Secondary Endpoint(s), Section 6.3.1 Additional Plasma PF-06954522 PK Parameters, Section 6.3.2 Plasma PF-06954522 PK Parameters During Food Effect Period, Section 6.3.4 Safety Summaries and PK Parameters During Japanese Cohort
CCI		

Population	Description	Applicable Analysis (for additional information refer to section 6)
CCI		

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 level, with data from different populations (e.g. non-Japanese and Japanese participants), if appropriate, reported separately. Each dietary allocation (i.e., standard and high fat breakfast) will also be reported separately.

If a dose level is repeated across 2 or more cohorts (within a dietary allocation), the data will be combined.

Unless otherwise stated the summary tables and/or statistical analyses may only include a single pooled placebo group across all included cohorts. Placebo will be pooled from all dose escalation periods but not the fed period or the Japanese cohort.

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.

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 treatment as a fixed effect and participant 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.

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 "<LLOQ", where LLOQ will be replaced with the value for the LLOQ.

In all exploratory biomarker (CCI) data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to the lower limit of quantification (LLOQ).

5.3.2. Deviations, Missing Concentrations and Anomalous Values

In PK and exploratory biomarker 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.

5.3.3. 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.

NOTE: For all analyses presented below **'by treatment'** refers to **by dose, population (if applicable) and dietary allocation (if applicable),** as described in Section 5.2, unless otherwise stated. Overall by population refers to reporting Japanese and Non-Japanese populations separately (i.e. Cohort 1 and Cohort 2 together, and Cohort 3 separately).

6.1. Primary Endpoint(s)

6.1.1. Adverse Events

AEs will be listed and summarized by treatment and overall by population 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 by population, 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 doses.

6.1.2. Clinical Safety Laboratory Data

Safety laboratory data will be listed and summarized by treatment and overall by population, 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 (or a participant's individual second dosing Period, for any participant that starts the study after Period 1), will be attributed to the dose 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). Any abnormality pre-dose in Period 1 or pre-dose at a participant's first dosing period would be reported as that participant's baseline measure for the period. Unplanned assessments will be included in summary abnormality tables and listings.

6.1.3. Vital Signs

Absolute values and changes from baseline (as defined in Section 3.1.3) in supine systolic and diastolic blood pressure, respiratory rate, temperature, 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.

Mean absolute values and mean changes from baseline for systolic and diastolic blood pressure, respiratory rate, temperature, and pulse rate will be plotted against time point. On each plot, there will be 1 line for each treatment with all doses 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 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.

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., for cohort 1, an occurrence pre-dose at Period 2 Day 1 will be attributed to the Period 1 dose). For any participant who starts the study after Period 1, the same considerations as described in Section 6.1.2 apply.

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.

6.1.4. 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.

6.1.5. Electrocardiograms

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 3.1.5.

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-06954522. 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 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.

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). For any participant who starts the study after Period 1, the same considerations as described in Section 6.1.2 apply.

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 assessment will be listed but will be excluded from safety summary except for categorical summaries.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined. The results of such analyses may not be included in the CSR.

6.1.6. Physical Examinations

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 Endpoint(s)

Plasma PK parameters for PF-06954522, as described in Section 3.2, will be listed and summarized descriptively by treatment and day, 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 and day (as appropriate) using the summary statistics as specified in the table below:

Table 5. Summary Statistics for PF-06954522 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, CV%, standard deviation, median, minimum, maximum.

*: if data permit

Supporting data from the estimation of AUC_{inf} and $t_{1/2}$ will be listed by dose: 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 treatment 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 treatment 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 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 coloured by treatment.

- individual concentration time plots by treatment (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.

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-06954522 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.

6.3. Other Endpoint(s)

6.3.1. Additional Plasma PF-06954522 PK Parameters

Additional plasma PK parameters for PF-06954522, as described in Section 3.3.1, will be listed and summarized descriptively, by treatment and day, as applicable, as described in Table 6 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 as applicable as required in the table below:

Table 6. Summary statistics to be produced for additional plasma PK Parameters for PF-06954522

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

Plots as described in Section 6.2 above will be produced. 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-06954522 PK Parameters During Food Effect Period (if conducted)

Plasma PK parameters for PF-06954522 in the 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.

A mixed effects ANOVA, as described in Section 5.2.3, will be performed separately on the natural log transformed AUC_{inf} (if data permit), AUC_{last}, and C_{max} (all dose-normalized prior to analysis, if appropriate) with dietary allocation included as a fixed effect and participant as a random effect, using only data from the respective periods that includes the two treatments of interest. The test treatment will be PF-06954522 administered with food in comparison to the reference treatment of PF-06954522 administered in the fasted state.

CCI

CCI

[redacted]

6.3.4. Safety Summaries and PK Parameters During Japanese Cohort (if conducted)

If conducted, PK parameters as described in Sections 3.2 and 3.3.1 and safety summaries as described in Section 3.1 will be reported separately for this cohort.

6.3.5. 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), by cohort and overall by population 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 treatment and overall by population and will show which participants were analyzed for PK, biomarkers and safety, which may not be produced in one table. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment.

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 provided in listings.

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.

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

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 / residual 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 (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 3. List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ANOVA	Analysis of variance
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
CCI	
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variation
DER	Dose Escalation Review
ECG	Electrocardiogram
FIH	First in Human
H	Hour
HR	Heart rate
ID	Identification
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
CCI	
PD	Pharmacodynamic
PE	Physical Examination

Abbreviation	Term
PK	Pharmacokinetic(s)
QTcF	corrected QT (Fridericia method)
REML	Restricted Maximum Likelihood
SAP	Statistical Analysis Plan
sec	Second
SoA	Schedule of Activities
TBD	To Be Determined
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to maximum observed concentration
$t_{½}$	Half life
V_z/F	Apparent volume of distribution