Protocol C4921001

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, 4-PERIOD, CROSSOVER, FIRST-IN-HUMAN STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SINGLE ASCENDING ORAL DOSES OF PF-07328948 ADMINISTERED TO HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan
(SAP)

Version: 2.0

Date: 09 May 2023

[redacted]

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 07 Nov 2022	Original: 02Sep2022 Amendment 1 29 Sept 2022	N/A	N/A
	CCI	[redacted]	[redacted]

2. INTRODUCTION

PF-07328948 is a small molecule allosteric inhibitor/degrader of BDK that is currently being developed as an oral therapy to treat heart failure.

Tissue and/or plasma BCAA and/or BCKA levels are elevated in various disease states including heart failure, type 2 diabetes mellitus, NAFLD/NASH, and obesity. Furthermore, elevated BCAA levels in HF are associated with a loss of the BCAA catabolic machinery, suggesting that the BCKDH pathway, involved in BCAA and BCKA catabolism, is dysregulated in cardiometabolic disease indications. Because inhibitory phosphorylation of BCKDH by BDK reduces BCAA catabolism, a BDK inhibitor would reduce BCKDH phosphorylation, thereby increasing BCAA and BCKA catabolism and reducing the elevated levels of BCAAs and BCKAs associated with several cardiovascular and metabolic diseases.

PF-07328948 is an orally administered, small molecule, potent allosteric BDK inhibitor that inhibits BCKDH phosphorylation in vitro and has consistently demonstrated robust, dose- and time-dependent BCAA and BCKA lowering in plasma and CCI *in mouse, rat and/or dog. In addition,* CCI [redacted]
These improvements were concomitant with reduced pBCKDH and BDK levels in heart and kidney CCI *as well as reduced plasma BCAA and BCKA levels.*

This study will be the first time PF-07328948 is administered to humans. The purpose of the study is to evaluate the safety, tolerability, plasma PK and PD of PF-07328948 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 this study - Study C4921001. 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

N/A.

2.2. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimand
	Primary:	*Primary:*	
Safety	• *To evaluate the safety and tolerability of single ascending doses of PF-07328948 administered orally to healthy adult participants.*	• *Assessment of adverse events, clinical safety laboratory tests, vital signs, continuous cardiac monitoring, 12-lead electrocardiograms, and physical examinations.*	N/A
	Secondary:	*Secondary:*	
PK	• *To evaluate the pharmacokinetics of PF-07328948 following single doses of PF-07328948 administered orally to healthy adult participants.*	• *PK parameters derived from plasma PF-07328948 concentrations: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}, and $t_{½}$.*	N/A
	Tertiary/Exploratory:	*Tertiary/Exploratory:*	
PK	• *To evaluate additional pharmacokinetic parameters of PF-07328948 following single doses of PF-07328948 administered orally to healthy adult participants.*	• *Additional PK parameters derived from plasma PF-07328948 concentrations: C_{max}(dn), AUC_{last}(dn) and if data permit AUC_{inf}(dn), CL/F and V_z/F.*	N/A
C Cl	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
PK	• *To evaluate the effect of food (eg, a protein-rich meal such as MMTT), if administered, on the plasma PK of PF-07328948 following single dose of PF-07328948 administered orally to healthy adult participants.*	• *PK parameters derived from plasma PF-07328948 concentrations after MMTT: C_{max}, T_{max}, AUC_{last}, and if data permit, AUC_{inf}, and $t_{½}$.*	N/A

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, sequential, crossover study of PF-07328948 administered to healthy adult participants.

The first 2 cohorts are planned, and the third cohort is optional. In each period, participants will be randomized to either PF-07328948 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-07328948 and up to 2 placebo.

Precautionary sentinel dosing will be used in any period evaluating escalating doses of PF-07328948 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, 2 participants (1 receiving PF-07328948 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.

In each cohort, a washout interval of at least 7 days will be introduced between subsequent doses.

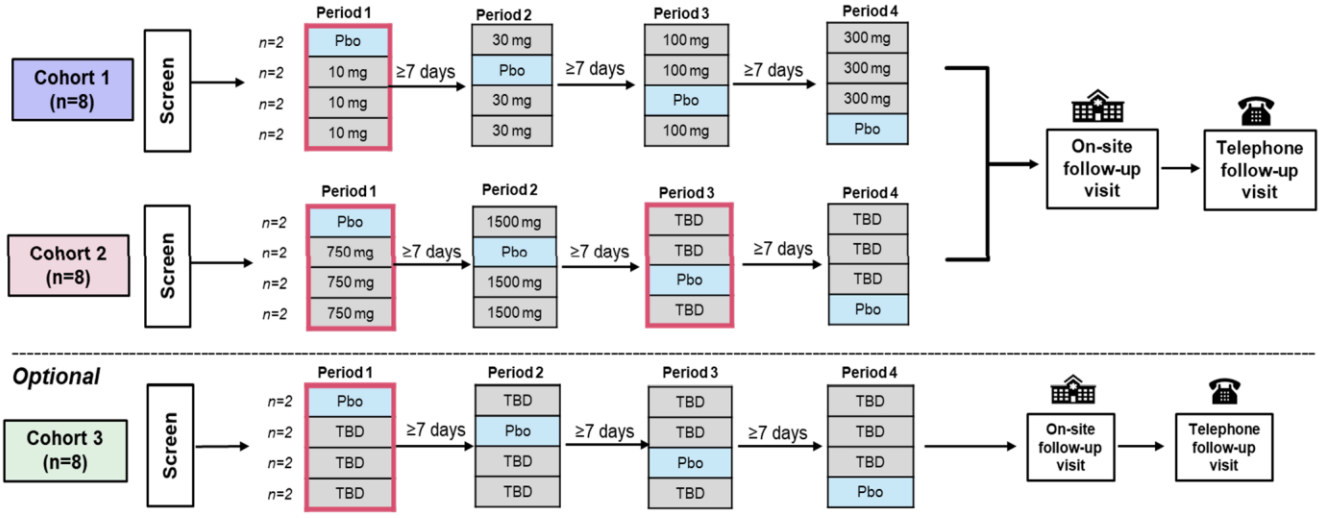
Based on the review of emerging safety, tolerability, and PK data (and PD data if available) in Cohorts 1 and 2, the optional third cohort may enroll 8 participants (crossover, placebo-controlled design) to explore additional doses, to repeat a dose, to evaluate split dosing, or to investigate food effects on PK CCI [redacted].

The effect of a high-protein meal on safety, tolerability, PK exposure, CCI [redacted] *may be assessed in at least 1 period within Cohort 2 and/or Cohort 3.*

If a participant drops out before completing all study periods within a cohort, or withdraws for a reason unrelated to safety, the participant may be replaced at the discretion of the investigator and sponsor. The replacement participant(s) may or may not be required to complete all periods of the cohort in which they are participating at the discretion of the investigator and sponsor.

Number of Participants: *Approximately 24 healthy adult participants (up to 3 cohorts of approximately 8 participants each) will be enrolled in this study.*

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. Effect of food (eg, a protein-rich meal such as MMTT) may be evaluated in at least 1 period of Cohort 2 (eg, P3) and/or Cohort 3

c. In the first period in each cohort (with red box) and the first period of assessment of food effect in any cohort (eg, P3 in Cohort 2 with red box), participants will be admitted on Day -2 and time-matched biomarker assessment will be collected on Day -1.

d. Precautionary sentinel dosing will be used in any period evaluating escalating doses of PF-07328948. For such periods, 2 participants (1 receiving PF-07328948 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)

As listed in Section 2.2, the primary endpoints are related to safety/tolerability and are described in Section 3.5.

3.2. Secondary Endpoint(s)

As listed in Section 2.2, the secondary endpoints are related to PK and are described in Section 3.3.1.

3.3. Other Endpoint(s)

3.3.1. PK Endpoints

Blood samples for PK analysis of PF-07328948 will be taken according to the Schedule of Activities given in the protocol.

The plasma PK parameters for PF-07328948, 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. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 2. Plasma PF-07328948 PK Parameters

Parameter	***Definition***	***Method of Determination***	**Analysis Scale**	**PF-07328948**
AUC_{last}	*Area under the plasma concentration-time curve from time 0 to the time of the* C_{last}	*Linear/Log trapezoidal method*	ln	D,A
AUC_{inf}*	*Area under the plasma concentration-time curve 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	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*	$Log_e(2)/k_{el}$*, 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
*CL/F**	*Apparent clearance*	$Dose/AUC_{inf}$	ln	D
*Vz/F**	*Apparent volume of distribution*	$Dose/(AUC_{inf} \cdot k_{el})$	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: D=displayed with descriptive statistics,
ln=natural-log transformed, R=raw (untransformed),
A=analysed using a statistical model (for specific treatment groups for evaluating food effect)
*=if data permits, dn = normalized to a 1mg PF-07321332 dose

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

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[redacted]

CCI [redacted]

3.4. Baseline Variables

Baseline for PD endpoints, laboratory data, vital signs and ECG are defined in Sections 3.3.2, 3.5.2, 3.5.3 and 3.5.4, respectively.

3.5. Safety Endpoints

3.5.1. 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 dosing day and time/start time, if collected, but before the end of the study will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

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

3.5.2. Laboratory Data

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

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 predose 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.

3.5.3. Vital Signs

Single assessment supine blood pressure and pulse rate measurements will be taken at screening, day 1 at hour 0, 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 given in the protocol. The average of the triplicate measurements will be calculated prior to analyzing the data. Respiratory rate will be measured as a single assessment at each timepoint specified in the protocol.

Baseline for these measures will be defined as the last predose 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.

3.5.4. 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 Schedule of Activities given 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 predose 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:

$QTcF = QT / (RR)^{1/3}$ where RR = 60/HR (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.

3.5.5. 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.

3.5.6. Physical Exam

Complete physical exam will be carried out at screening or upon admission for a participants 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 data 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.

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.

Table 3. Analysis Sets

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 6.6 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 6.3.1 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 6.3.1 PK Endpoints
CCI [redacted]	[redacted]	[redacted]

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no formal statistical hypotheses or decision rules in this study.

5.2. General Methods

Unless otherwise stated, all summaries and plots will be presented by treatment. If a dose level is repeated across 2 or more cohorts, the data will be combined, unless the dose is in a different food state (e.g. after an MMTT), 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. Placebo will be pooled from all dose escalation periods but not the fed period.

5.2.1. Analyses for Continuous Endpoints

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

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

5.2.2. Analyses for Categorical Endpoints

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

5.2.3. Mixed Model for Repeated Measurements (MMRM)

An MMRM model will be used with treatment, time (as a factor), treatment-by-time interaction, baseline and baseline-by-time interaction as fixed effects. Time will be fitted as a repeated effect within each participant*period. Baseline will be included as two separate variables, the average baseline for the participant, and the deviation of each treatment period baseline from the average baseline for each participant. An unstructured covariance matrix will be fitted to the repeated times within participant (other covariance matrices will be considered if necessary, e.g. if the model does not converge).

The Least Squares (LS) means (and standard errors, 90% confidence intervals and 2-sided p-values) will be obtained for each treatment at each timepoint. Differences (and standard errors, 90% confidence intervals and 2-sided p-values) between LS means will also be obtained, comparing each dose versus placebo. If data have been logged, LS means and differences (including CI's) will be back transformed to give percent changes from baseline ([relative change from baseline -1]*100), and percent change from placebo ([ratio of relative change from baseline -1]*100).

Example SAS code is provided in Appendix 2.

Statistical Model Diagnostics

The presence of outliers will be investigated for this model. An outlier will be defined as any response data value with a studentized (conditional) residual greater than 3, or less than -3. A listing will be presented of any participants meeting these criteria and will be included with standard SAS output. The assumptions of normality will be verified graphically using residual plots. For each fitted model, a set of conditional studentized residual plots will be produced, including residual plot, histogram of normality, quartile-quartile (QQ) plot and summary of fit statistics. The residual plots will not be included in the CSR.

If there are outliers or major deviations from normality, 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.

5.2.4. Mixed Effects Analysis of Variance (ANOVA)

A mixed effects ANOVA with treatment as a fixed effect and participant as a random effect will be used for the analysis of PK endpoints.

Least square (LS) estimates of the group means and mean differences along with standard errors, 90% confidence intervals and p-values will be presented, which will be back-transformed for data that was natural log-transformed prior to analysis.

A figure showing the (back-transformed) LS means (with 90% confidence intervals) vs group will be produced.

Example SAS code is provided in Appendix 2.

Statistical model diagnostics as described in Section 5.2.3 would also be conducted for these analyses.

5.2.5. Mixed Effects ANCOVA

A mixed effects model with treatment as a fixed effect, baseline as a covariate and participant as a random effect will be used. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

Example SAS code is provided in Appendix 2.

Statistical model diagnostics as described in Section 5.2.3 would also be conducted for these analyses.

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

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

1. A concentration has been collected as ND (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.

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

The primary endpoints are related to safety/tolerability and their analyses are described in Section 6.6.

6.2. Secondary Endpoint(s)

The secondary endpoints as listed in Section 2.2 are related to PK and their analyses are described in Section 6.3.1.

6.3. Other Endpoints

6.3.1. PK Endpoints

The 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. Each PK parameter will be summarized by dose (and fasting condition, if appropriate) as applicable. Each summary will include the set of summary statistics as specified in Table 4.

Table 4. PK Parameters to be Summarized Descriptively

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

The plasma PK parameters will be summarized descriptively by dose (and fasting condition, if appropriate) as applicable. Dose-normalized AUC_{inf}, AUC_{last}, and C_{max} will be plotted against dose (and fasting condition, if appropriate) using a logarithmic scale, and will include individual participant values and the geometric means for each dose. These plots will be used to understand the relationship between the PK parameters and dose (and fasting condition, if appropriate).

Geometric means will have a different symbol than the individual values. A footnote will be added to the plots to indicate that geometric means are presented. All dose normalized parameters will be listed along with other individual PK parameters.

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

Presentations for PF-07328948 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 nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

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

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

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

- 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), coloured by dose.

- mean concentration-time plots (on both linear and semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose), coloured by 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-07328948 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.

If the food effect is assessed the PK parameters will also be summarized descriptively as described above by fasting condition.

To assess any effect of food in Cohort 2 and/or Cohort 3, *a mixed effects ANOVA 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 5.2.4. If performed, only data from the respective periods that includes the two treatments of interest will be included. The Kenward-Roger adjustment for the degrees of freedom will be used. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for these differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for these ratios. The treatment in the fasted state will be the reference and the test treatment will be in the fed state.

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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 summarised overall in accordance with the sponsor reporting standards.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition by treatment, 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. 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.

6.6. Safety Summaries and Analyses

All safety analyses will be performed on the Safety Analysis Set.

6.6.1. Adverse Events

Adverse events will be listed and summarized by treatment and overall, in accordance with sponsor reporting standards using the safety analysis set defined in Section 4.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards using the safety analysis set defined in Section 4. Baseline is as defined in Section 3.5.2.

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.

6.6.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure, pulse rate and respiratory rate will be summarized by treatment and timepoint, according to sponsor reporting standards, using the safety analysis set defined in Section 4. Baseline is as defined in Section 3.5.3.

Mean changes from baseline for supine systolic and diastolic blood pressure, pulse rateand respiratory rate will be plotted against time post-dose. On each plot there will be one line for each treatment. Dats from all cohorts will be plotted on the same figure using a single line for the placebo group(s). 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 blood pressures, pulse rate and respiratory rate will be summarized by treatment, according to sponsor reporting standards.

Minimum and/or maximum absolute values and changes from baseline for supine vital signs will also be summarized descriptively by treatment using categories as defined in Appendix 1.

Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time points will be counted in these categorical summaries.

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.

6.6.4. 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 3.5.4.

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-07328948. 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, PR and QRS) 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 postdose time points will be counted in these categorical summaries.

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.

6.6.5. 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.

6.6.6. 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 and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

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

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. However, as this is a sponsor-open study, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety and tolerability assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team.

7.2. Interim Analyses and Summaries

N/A

8. REFERENCES

Pfizer Guidance for Evaluation of QT / QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs; Members of the Cardiovascular Safety & Advisory Council (CVSAC); January 26, 2018

APPENDICES

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

Categories for QTcF

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

Categories for PR and QRS

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

Categories for Vital Signs

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

Appendix 2. Example SAS Code for Statistical Analyses

CCI

Mixed Effects ANOVA: (PK parameters)

```
proc mixed data = dataset method = ml;
      class subjid treattxt;
      model &var = treattxt /residual;
      random subjid;
      lsmeans treattxt / diff cl alpha = 0.1;
run;
```

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CCI [redacted]	[redacted]
BCAA	branched-chain amino acid
BCKA	branched-chain ketoacid
BCKDH	branched-chain ketoacid dehydrogenase
BDK	branched chain ketoacid dehydrogenase kinase
BLQ	below the limit of quantitation
BP	blood pressure
CI	confidence interval
C_{max}	maximum observed concentration
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
FDA	Food and Drug Administration (United States)
HR	Heart Rate
LLOQ	lower limit of quantitation
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MMRM	mixed-effects model with repeated measures
MMTT	Mixed Meal Tolerance Test
N/A	not applicable
CCI [redacted]	[redacted]
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
ULN	upper limit of normal