Protocol C4171001

A PHASE 1, 3-PART, SPONSOR OPEN STUDY OF PF-07202954 IN HEALTHY ADULTS: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TO ASSESS SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE (IN PART 1), AND REPEATED (IN PART 2), ESCALATING, ORAL DOSES ALONG WITH CONDITIONAL PART 3 OF RANDOMIZED, OPEN-LABEL ASSESSMENT OF EFFECT OF FOOD ON PF-07202954 EXPOSURE

Statistical Analysis Plan
(SAP)

Version: **1**

Date: 19Mar2021

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APPENDICES

1. VERSION HISTORY

TABLE 1. SUMMARY OF CHANGES

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1 19 March 2021	Protocol Amendment 1 01 Dec 2020	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 C4171001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Table 2 outlines the key objectives and endpoints for Part 1, Part 2, and Part 3 (if conducted) of this study. There are no estimands for this study.

TABLE 2. KEY OBJECTIVES AND ENDPOINTS IN STUDY C4171001

Study	Objectives	Endpoints
Part 1		
Primary	To evaluate **safety and tolerability** of **single**, oral, escalating doses of PF-07202954 administered with a standard morning meal in healthy, adult participants.	Following assessments over ≥10 days of **each** Period **and** up to Day 30 ±2 days post last dose of study intervention – • AEs; • Clinical laboratory tests; • Vital signs (including BP and pulse rate); • Cardiac conduction intervals via 12-lead ECG.
Secondary	To characterize the **plasma PK** profile of PF-07202954 following administration of **single**, oral, escalating doses.	PK parameters[a] derived from plasma PF-07202954 concentrations: • C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{½}$, as data permit.
Part 2		
Primary	To evaluate **safety and tolerability** of **repeated,** oral, escalating doses of PF-07202954 administered with a standard morning meal in healthy, adult participants with simple hepatic steatosis.	Following assessments over the duration of dosing **and** up to Day 30 ±2 days post last dose of study intervention – • AEs; • Clinical laboratory tests; • Vital signs (including BP and pulse rate); • Cardiac conduction intervals via 12-lead ECG.

Secondary	To characterize the **plasma and urine PK** profiles of PF-07202954 following administration of **repeated**, oral, escalating doses.	PK parameters[a] derived from plasma PF-07202954 concentrations:
		• Single dose: C_{max}, T_{max}, AUC_{tau} on Day 1.
		•
		• Repeated dose:
		  • Days 7 and 14 – C_{max}, T_{max}, AUC_{tau}, as data permit.
		  • Day 14 – $t_{½}$ as data permit.

TABLE 2. KEY OBJECTIVES AND ENDPOINTS IN STUDY C4171001

Study	Objectives	Endpoints
		PK parameters[a] derived from urine PF-07202954 concentrations on **Day 14**: Ae_{tau}, Ae_{tau}%, CL_r.
Part 3, if conducted		
Primary	To characterize the effect of a **high-fat/high-caloric meal,** compared to following an overnight fast, on **plasma PK** profile of PF-07202954 following administration of a single oral dose to healthy adults.	PK parameters[a] derived from plasma PF-07202954 concentration: • C_{max}, T_{max}, AUC_{last}, and AUC_{inf}, as data permit.
Secondary	To evaluate **safety and tolerability** of a **single**, oral, dose of PF-07202954 administered with a high-fat/high-caloric meal compared to following an overnight fast.	Following assessments over ≥5 days of **each** Period **and** up to Day 30 ±2 days post last dose of study intervention – • AEs; • Clinical laboratory tests; • Vital signs (including BP and pulse rate); • Cardiac conduction intervals via 12-lead ECG.

a. For a complete definition of all PK parameters refer to Table 4 and Table 5.

NOTE: For all non-PK related endpoints, **baseline is defined** as the time-matched data obtained while on placebo [Part 1], 0H assessment on Day 1 or 0-12H or 0-24H assessment prior to 1st dose [Part 2], **or** 0H assessment on Day 1 in each Period [Part 3]. Any deviations to these definitions are described in Section 3 of this SAP.

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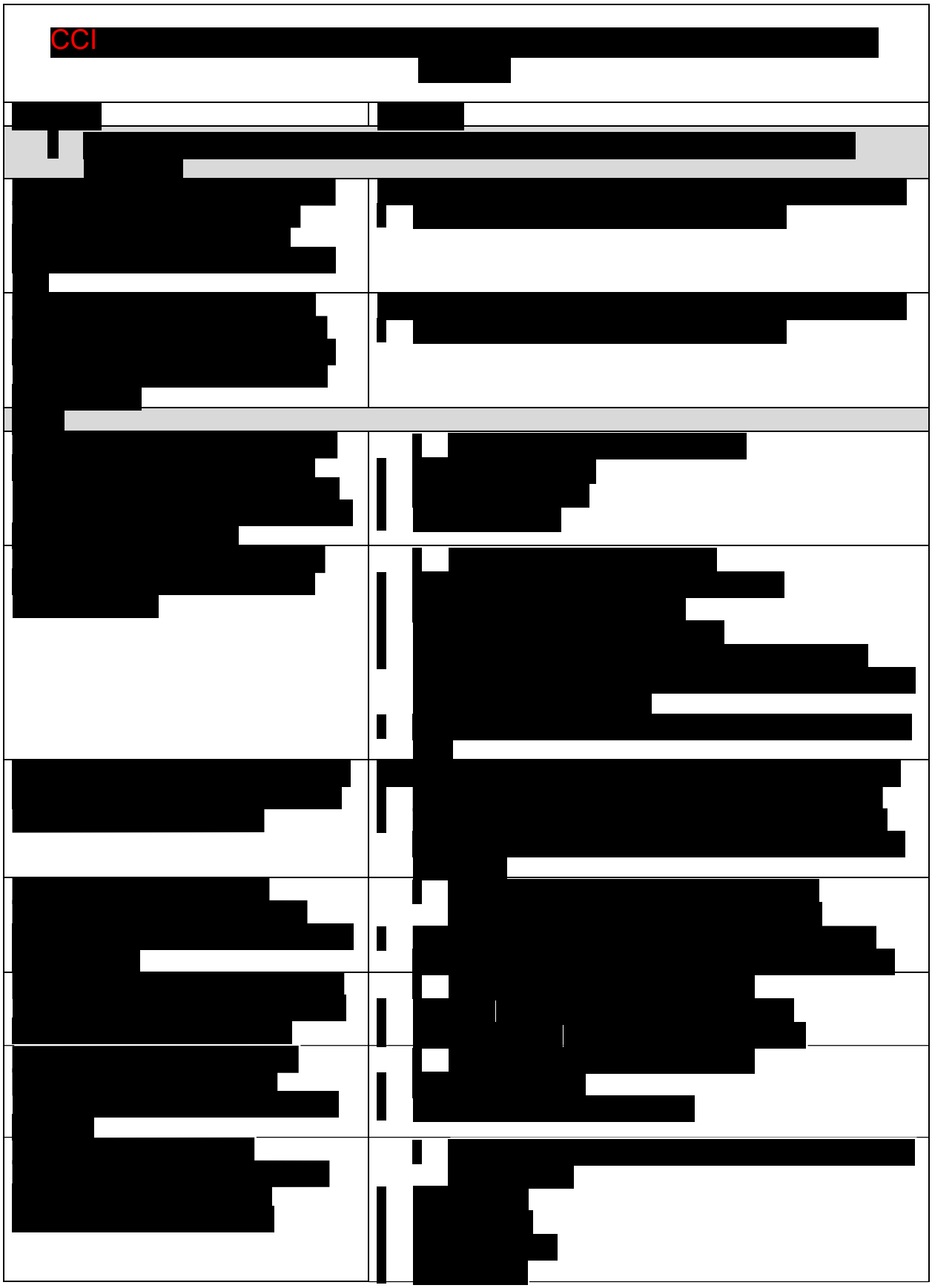
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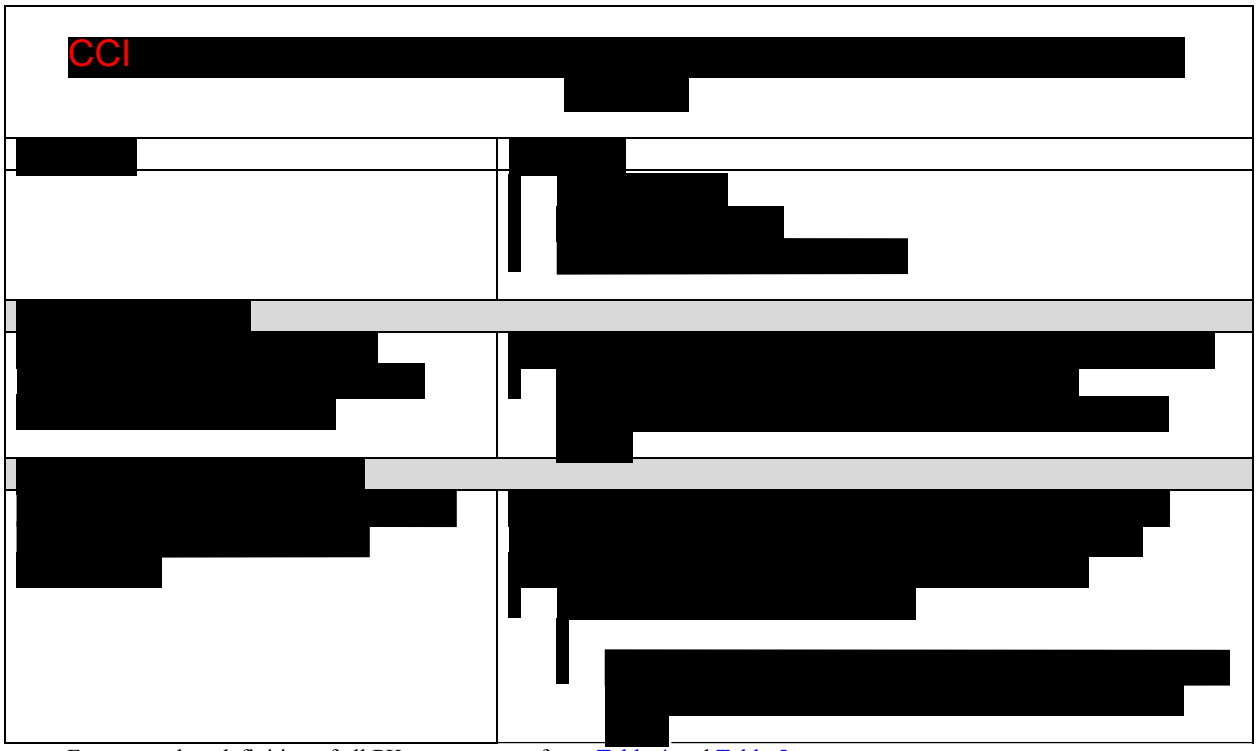


a. For a complete definition of all PK parameters refer to Table 4 and Table 5.

NOTE: For all non-PK related endpoints, **baseline is defined** as the time-matched data obtained while on placebo [Part 1], 0H assessment on Day 1 or 0-12H or 0-24H assessment prior to 1st dose [Part 2], **or** 0H assessment on Day 1 in each Period [Part 3]. Any deviations to these definitions are described in Section 3 of this SAP.

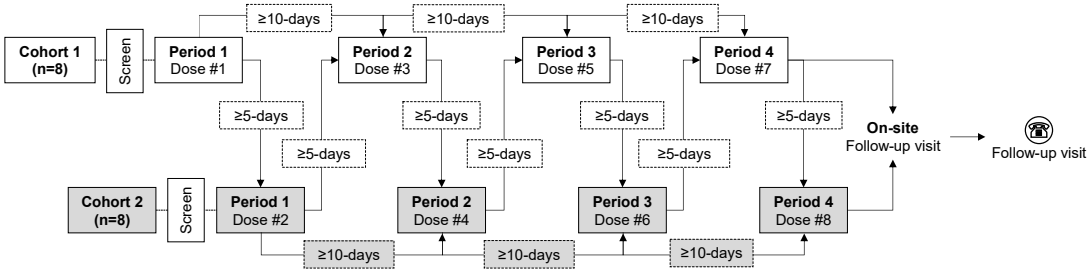
2.2. Study Design

The study is planned as a 3-part design with investigator- and participant-blinded (sponsor-open), placebo-controlled, randomized, dose-escalation in Part 1 and Part 2; and a randomized, open-label design, in Part 3 (if conducted). Participants will receive oral dose(s) of PF-07202954 and/or placebo in this study. A total of up to 88 unique participants (16 in Part 1, up to 30-40 initially in Part 2 [and potential expansion to 50-60 post formal IA and protocol amendment], and a maximum of 12 in Part 3) are planned to be randomized in this study.

The set-up of each of the 3 Parts of this study are summarized in Figure 1 (Part 1), Figure 2 (Part 2) and Figure 3 (Part 3).

Figure 1. Overall Study Design - Part 1

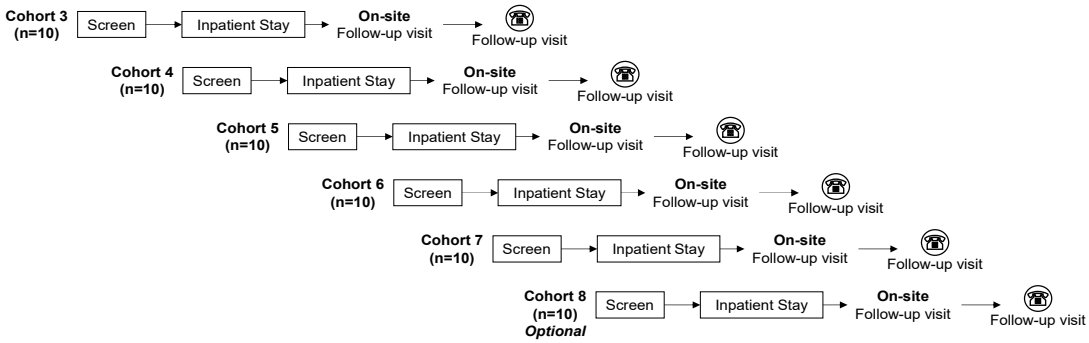
Part 1: Sample size (N) = 16 participants
Randomized, double-blind (Sponsor-open), 4-period, inter-leaving, placebo-controlled, ***single, oral dose, escalating*** design



- Screen to dosing on Day 1 in Period 1: maximum of 28 days
- Inpatient stay in **each** Period: Day -1 to minimum of Day 4 (ie, 72H post dose)
- In **each** Period, 6 participants randomized to receive PF-07202954, and 2 participants will receive matching-placebo with standard morning meal
- Intervals of ≥x-days reflect number of days between ***dosing*** *either* between Cohorts (ie, ≥5-days) **or** within a given Cohort (ie, ≥10-days)
- On-site Follow-up visit to occur 8±2 days, with *an additional* telephone contact at 30±2 days, post last dose of study intervention

Figure 2. Overall Study Design - Part 2

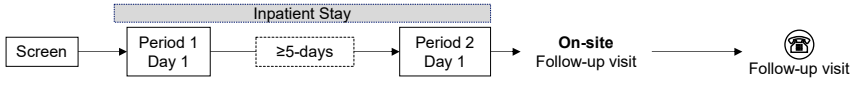
Part 2: Sample size (N) = 50 in 1st planned 5 Cohorts and up to 60 including 1 optional Cohort of participants
Randomized, double-blind (Sponsor-open), placebo-controlled, sequential, ***repeated, oral dose, escalating*** design



- **Screen to Day 1:** maximum of 28 days includes ***double confirmation*** of CAP ≥ 270 dB/m *and* VCTE < 7 kPa on FibroScan® on ***separate*** days
- **Inpatient stay:** Day -2 to Day 17 (19 consecutive days with 18 nights)
  - Baseline for safety (**at 0H** prior to dosing on **Day 1**), other markers of *clinical activity* (on **Day -1**), CCI
- In **each** cohort, 8 participants will be randomized to receive PF-07202954, and 2 participants will receive placebo
- ***Once-daily*** dosing to occur from Day 1 to Day 14, inclusive, with a standard morning meal
- On-site Follow-up visit to occur 8±2 days, with *an additional* telephone contact at 30±2 days, post last dose of study intervention

Figure 3. Overall Study Design - Part 3 [if conducted]

Part 3 *[if conducted]***:** Sample size (N) = ≤ 12 participants
Randomized, open-label, 2-period, crossover, single oral dose of PF-07202954 administered with and without ***high-fat/high-caloric meal***



- Screen to Day 1 in Period 1: maximum of 28 days
- Inpatient stay: Continuous from Day -1 (in Period 1) to Day 4 (in Period 2) – a total of 10 days and 9 nights
- On-site Follow-up visit to occur 8±2 days, with *an additional* telephone contact at 30±2 days, post last dose of study intervention

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

As listed in Section 2.1 the primary endpoints in Part 1 and Part 2 are related to safety/tolerability which are described in Section 3.5. The primary endpoints in Part 3 are the plasma PK endpoints which are described in Section 3.3.

3.2. Secondary Endpoint(s)

The secondary endpoints (in Part 1 and Part 2) are related to PK and are described in Section 3.3. The secondary endpoints in Part 3 are related to safety/tolerability which are described in Section 3.5.

3.3. Other Endpoint(s)

3.3.1. Pharmacokinetic (PK) Endpoints

The PK parameters for PF-07202954 following oral dose administration will be derived from the plasma concentration-time profiles and urine concentrations as detailed in Table 4 [following single doses in Part 1 and Part 3] and Table 5 [following single and repeated doses in Part 2].

In all cases, actual PK sampling times will be used in the derivation of PK parameters. In the event that the actual sampling time is not available, the nominal time may be used if there is no evidence that the actual sampling time deviates substantially from the nominal time.

TABLE 4. PLASMA PK PARAMETERS FOR PART 1 (SINGLE, ESCALATING DOSES) AND PART 3 (SINGLE DOSE FOOD EFFECT, IF CONDUCTED)

Parameter	Definition	Method of Determination
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
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
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
T_{lag}	Lag time	Observed directly from data as time prior to the time corresponding to the first quantifiable concentration.
$t_{1/2}$*	Terminal 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.
CL/F*	Apparent clearance	$Dose/AUC_{inf}$
V_z/F*	Apparent volume of distribution	$Dose/(AUC_{inf} \times k_{el})$
CCI [redacted]	[redacted]	[redacted]

TABLE 4. PLASMA PK PARAMETERS FOR PART 1 (SINGLE, ESCALATING DOSES) AND PART 3 (SINGLE DOSE FOOD EFFECT, IF CONDUCTED)

Parameter	Definition	Method of Determination
CCI [redacted]	[redacted]	[redacted]

*As data permit

TABLE 5. PLASMA AND URINE PK PARAMETERS FOR PART 2 (REPEATED ESCALATING DOSES)

Parameter	Day(s)	Definition	Method of Determination
Plasma			
AUC_{tau}	1, 7, 14	Area under the plasma concentration-time profile from time 0 to time τ (tau)	Linear/Log trapezoidal method
C_{max}	1, 7, 14	Maximum observed concentration during the dosing interval	Observed directly from data
T_{max}	1, 7, 14	Time for C_{max}	Observed directly from data as time of first occurrence
T_{lag}	1, 7, 14	Lag time	Observed directly from data as time prior to the time corresponding to the first quantifiable concentration
C_{min}	7, 14	Minimum observed concentration during the dosing interval	Observed directly from data
C_{av}	7, 14	Average concentration	AUC_{tau}/tau
PTR	7, 14	Peak-to-trough ratio	C_{max}/C_{min}
$R_{ac,AUCtau}$	7, 14	Observed accumulation ratio	AUC_{tau} (Day 7 or 14)/AUC_{tau} (Day 1)
$R_{ac,Cmax}$	7, 14	Observed accumulation ratio for C_{max}	C_{max} (Day 7 or 14)/C_{max} (Day 1)
$t_{1/2}$*	14	Terminal half-life	$Log_e(2)/k_{el}$, • where k_{el} is terminal phase rate constant calculated by a linear regression of log-linear concentration-time curve. • only those data points judged to describe terminal log-linear decline will be used in the regression.
V_z/F*	14	Apparent volume of distribution	$Dose/(AUC_{tau} \times k_{el})$
CL/F	7, 14	Apparent clearance	$Dose/AUC_{tau}$
CCI [redacted]	[redacted]	[redacted]	[redacted]
Urine			
Ae_{tau}	14	Amount of unchanged drug recovered in urine during dosing interval	Sum of [urine concentration x urine volume] for each collection over the dosing interval
Ae_{tau}%	14	Percent of dose recovered in urine as unchanged drug over dosing interval	100 x Ae_{tau}/Dose
CL_r	14	Renal clearance	Ae_{tau}/AUC_{tau}

*As data permit

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3.4. Baseline Variables

Baseline variables are those collected only prior to dosing. In this study baseline variables are the demographic data of age, race, weight, and body mass index which will be collected at screening and summarized by treatment in accordance with the sponsor reporting standards.

3.5. Safety Endpoints

The primary assessments include the standard safety endpoints listed below (see the protocol for collection days and list of parameters):

- Treatment-emergent AEs;
- Clinical laboratory tests;
- Vital signs (including BP and pulse rate);
- Cardiac conduction intervals via 12-lead ECG.

These endpoints will be summarized according to CDISC standards described in the CDISC Safety Rulebook[1].

3.5.1. Treatment Emergent Adverse Events

Any events occurring following start of treatment (either PF-07202954 or placebo) will be counted as treatment emergent. Events that occur in a non-treatment period (i.e. follow-up) within the lag time of 28 days will be counted as treatment emergent and attributed to the previous treatment taken. Similarly, the time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

3.5.2. Laboratory Data

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

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. Post-baseline assessments will not take into account whether each subject's *baseline* test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline is defined as the time-matched data obtained while on placebo [Part 1], 0H assessment on Day 1 [Part 2], ***or*** closest to 0H assessment prior to dosing on Day 1 in *each* Period [Part 3]. Results from only the planned study visits will be considered for baseline assessment.

3.5.3. Vital Signs

Single supine blood pressure and pulse measurements will be taken at all time points listed in the Schedule of Activities given in the protocol. ***Baseline is defined*** as the time-matched data obtained while on placebo [Part 1], 0H assessment on Day 1 [Part 2], ***or*** 0H assessment on Day 1 in *each* Period [Part 3].

The following vital signs endpoints will be determined for each subject:

- The maximum decrease and increase from baseline over all measurements taken postdose for systolic and diastolic blood pressures.
- The maximum increase from baseline over all measurements taken postdose for pulse rate.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each postdose measurement to give the change from baseline. The maximum of these values over the respective period (Part 1 and Part 3) or entire study (Part 2) will then be selected, except in the case where a subject 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 largest negative value of the changes from baseline. In cases where a subject does not show a decrease, the minimum increase should be taken.

3.5.4. ECG

Single and triplicate 12-lead ECGs will be obtained on all subjects at times 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. ***Baseline is defined*** as the average of the time-matched triplicate data obtained while on placebo [Part 1], the average of the triplicate collected at 0H assessment prior to dosing on Day 1 [Part 2], ***or*** the 0H predose assessment on Day 1 in *each* Period [Part 3].

The QT, QTcF, PR, QRS and heart rate will be recorded at each assessment time.

If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

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

The maximum absolute value (postdose) and the maximum increase from baseline for QTcF, PR and QRS, will be determined over all measurements for each subject.

The maximum increase from baseline will be calculated by firstly subtracting the baseline value from each postdose measurement to give the change from baseline. The maximum of these values over the respective period (Part 1 and Part 3) or entire study (Part 2) will then be selected, except in the case where a subject does not show an increase. In such an instance, the minimum decrease should be taken.

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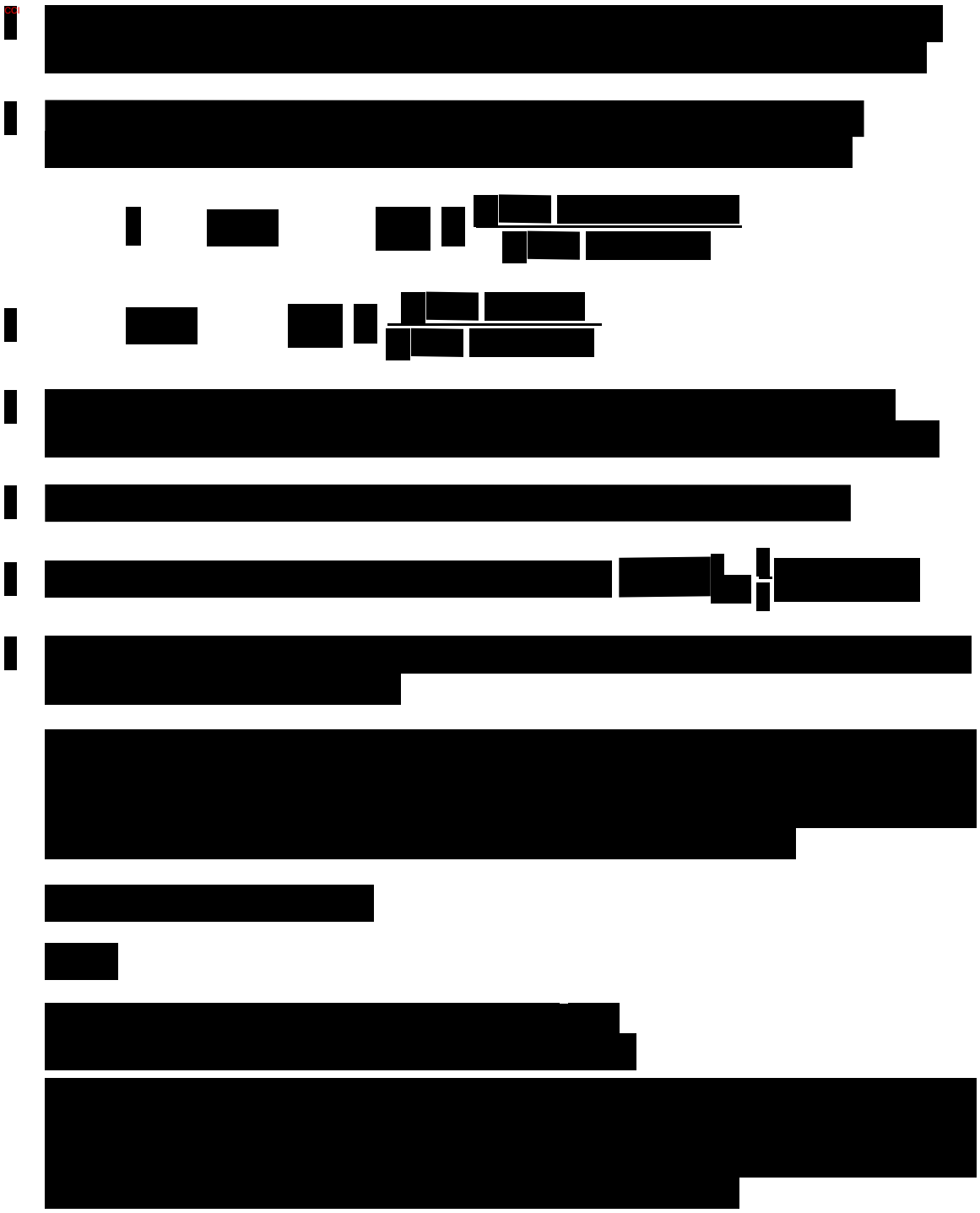

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, the analyses sets are defined as outlined in Table 6.

TABLE 6. DEFINITION OF THE ANALYSES SETS IN STUDY C4171001

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and randomization: • 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.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention for the given Part (1, 2, or 3).
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention for the given Part (1, 2 or 3). Participants will be analyzed according to the product they actually received.
PK Concentration	All participants who receive at least 1 dose of PF-07202954 and in whom at least 1 PK concentration is reported, for the given Part (1, 2, or 3).
PK Parameter	All participants who receive at least 1 dose of PF-07202954 and who have at least 1 of the PK parameters of interest calculated, for the given Part (1, 2, or 3).

5. GENERAL METHODOLOGY AND CONVENTIONS

This is a 3-part sponsor-open study with Part 1 and Part 2 as investigator and participant blinded. Specific Pfizer personnel (analytical staff, medical monitor, clinical leads, clinicians, statistician, programmers, data managers and pharmacokineticists and people shadowing these team members) will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data. Treatment randomization information will be kept confidential by Pfizer personnel and will not be released to the investigator/site staff until the conclusion of the study. Final analysis will follow the official database release after completion of all parts of the study.

5.1. Hypotheses and Decision Rules

There are no statistical hypotheses or decision rules.

5.2. General Methods

Descriptive Statistics

Descriptive statistics, including the sample size, mean, standard deviation, median, minimum, and maximum values, will be provided for continuous endpoints. For binary/categorical variables the number and proportion of participants achieving the thresholds will be presented. Some measures will be summarized using graphical representations by treatment and study day of visit, where appropriate.

Mixed Effect Analysis of Variance (ANOVA)

The mixed effect ANOVA model will be used to assess the food effect in Part 1 or Part 3, CCI [redacted] For endpoints in Part 1 of the study treatment group will be the fixed effect and participant will be the random effect. In Part 3, sequence, period and treatment will be the fixed effects and participant within sequence will be the random effect. Estimates of treatment effects will be assessed using the least square means (LSMs) and 80% Confidence Intervals (CIs). Estimates of the mean differences between each active dose and placebo, and the corresponding 80% CI will be obtained from the model. If there are major deviations from the statistical assumptions underlying this model then non-parametric analyses may be presented.

Analysis of Covariance (ANCOVA)

The ANCOVA model will be used with continuous endpoints for landmark (single time point) analyses. The model will include treatment group as a fixed effect, baseline value of the endpoint being analyzed as a covariate. Study site and interaction of study site with treatment will be considered to be included as potential covariates for the analysis of whole liver fat only. Estimates of treatment effects will be assessed using the least square means (LSMs) and 80% Confidence Intervals (CIs). Estimates of the mean differences between each active dose and placebo, and the corresponding 80% CI will be obtained from the model. If there are major deviations from the statistical assumptions underlying this model then alternative transformations or non-parametric analyses may be presented. Justification for any alternative to the planned analysis will be given in the study report.

Mixed Model for Repeated Measurements (MMRM)

This model will be used for the analysis of endpoints with more than one post-baseline collection time point. All observed data collected during the post-baseline treatment period up to and including 1st Follow-up visit (conducted onsite) in Part 2 will be utilized; data collected during the follow-up period will be excluded. Early discontinuation data will also be excluded. The MMRM analysis will be performed with treatment, study day and treatment-by-study day interaction as fixed effects, baseline value as a covariate. Repeated measures model with unstructured correlation matrix will be utilized. Time will be fitted as a repeated effect. If this does not converge then compound symmetry structure will be considered. Estimates of treatment effects will be assessed using LSMs and 80% CIs at each time point. LSM difference between each dose of PF-07202954 and placebo group along with the 80% CIs and 2-sided p-values will be provided. If there are major deviations from the statistical assumptions underlying this model then alternative transformations (e.g. log) or non-parametric analyses may be presented. Justification for any alternative to the planned analysis will be given in the study report.

Non-parametric Analysis

If the data have many outliers even after the log-transformation the following non-parametric analysis will be performed instead of the linear model. An outlier will be defined as any datapoint falling outside of 3.5 × standard deviations +/- the median. Additional evaluative

statistics will be conducted to explore the nature of the outliers in order to determine the appropriateness of a parametric analysis.

For group medians 80% CIs will be presented. In addition, the 80% CIs will also be presented for differences in group medians from placebo group median. The method of McGill, Tukey, and Larson[2] will be employed to calculate the CI for the difference in treatment group medians.

Dose Response Modeling

Data permitting a 4-Parameter E_{max} model will be used to characterize the %change from baseline dose-response relationship of whole liver fat in Part 2. The model structure will take the form:

$$CFB = E_0 + \frac{E_{max} \times dose^{Hill}}{ED_{50}{}^{Hill} + dose^{Hill}}$$

E_0 is the placebo effect, *dose* is the target randomized dose, E_{max} is the maximum effect, ED_{50} is the dose producing 50% of the maximum effect and *Hill* is the slope parameter.

The natural log transformed relative ratio from baseline response at the end of treatment period will be modeled with dose as a continuous variable and natural log transformed baseline whole liver fat as a covariate. The model will be applied to the LSMean results from the primary ANCOVA model utilizing a Bayesian methodology with weakly informative priors as described in Appendix 3. The posterior means and 80% credible intervals of the placebo-adjusted effect estimates at each dose will be exponentiated to obtain the predicted values of %change from baseline. Estimates of the model parameters of E_0, E_{max}, ED_{50} and slope and their 80% credible intervals will also be produced. In addition, the doses that result in 25% and 30% liver fat lowering will be identified along with their 80% credible intervals.

If convergence cannot be obtained or visual inspection of the data does not support a dose-response E_{max} relationship the following options will be considered in order: (1) assume the hill parameter is 1 and remove from the model (giving a 3-parameter dose-response E_{max} model) or (2) utilize alternative priors to those provided in the appendix.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data:

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

5.3.2. Pharmacokinetics Data:

Methods to handle missing PK data are described below.

Concentrations Below the Limit of Quantification:

In all 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.)

Deviations, Missing Concentrations and Anomalous Values:

In summary tables and plots of 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.

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

Pharmacokinetic Parameters:

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a subject'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 subject 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 or at least 50% of the data are available depending on the parameter.

If an individual subject 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 from the gastrointestinal tract), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

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6. ANALYSES AND SUMMARIES

The data from each of the 3 Parts will be analyzed and reported separately in a single CSR issued at the end of this study.

6.1. Primary Endpoint(s)

The primary endpoints in Part 1 and Part 2 are related to safety/tolerability whose analyses are described Section 6.6.

The primary endpoints in Part 3 are the plasma PK endpoints whose analyses are described in Section 6.2.

6.2. Secondary Endpoint(s)

The secondary endpoints (in Part 1 and Part 2) as well as the primary endpoints (in Part 3) are related to PK and are described herein. The following analyses will utilize the PK Concentration and PK Parameter analyses sets defined in Table 6 in Section 4.

No formal inferential statistics will be applied to the plasma PK data from Part 1 and 2. In Part 3, if conducted, the statistical comparison of plasma PK under high-fat/high-caloric state (test) versus fasted (reference) condition is envisioned.

Plasma parameters will be summarized using the descriptive statistics specified in Table 7 and urine PK parameters will be summarized using the statistics specified in Table 8.

TABLE 7. PLASMA PK PARAMETERS TO BE SUMMARIZED DESCRIPTIVELY

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, C_{max}, AUC_{inf}(dn), AUC_{last}(dn), AUC_{tau}, AUC_{tau}(dn), C_{max}(dn), CL/F, V_z/F, C_{min}, PTR, AUC_{tau}, C_{av}, $R_{ac,AUCtau}$, and $R_{ac,Cmax}$	N, arithmetic mean, median, %CV, standard deviation (SD), minimum (min), maximum (max), geometric mean and geometric %CV
T_{max}, T_{lag}	N, median, min, max.
t½	N, arithmetic mean, median, %CV, SD, min, max.

TABLE 8. URINE PK PARAMETERS TO BE SUMMARIZED DESCRIPTIVELY

Parameter	Summary Statistics
Ae_{tau}, Ae_{tau}% and CL_r	N, arithmetic mean, median, %CV, SD, min, max, geometric mean and geometric %CV.

- **Part 1 (Single, Escalating Doses):**

- Plasma concentrations of PF-07202954 will be descriptively summarized and plotted by nominal PK sampling time and dose.

- The plasma PK parameters AUC_{inf}, C_{max}, AUC_{last}, T_{max}, T_{lag}, CL/F, V_z/F, and $t_{½}$ will be summarized descriptively by dose;

[redacted]

- **Part 2 (Repeated, Escalating Doses):**

- Plasma concentrations of PF-07202954 will be descriptively summarized and plotted by nominal PK sampling time, day, and dose:

- The plasma PK parameters AUC_{tau}, C_{max}, T_{max}, T_{lag}, $t_{½}$, C_{min}, C_{av}, PTR, CL/F, V_z/F, $R_{ac,AUCtau}$, and $R_{ac,Cmax}$, and the urine PK parameters Ae_{tau}, Ae_{tau}%, and CL_r will be summarized descriptively by dose and day as applicable;

[redacted]

- Median morning trough (predose) plasma concentrations will be plotted by day (all doses on the same plot) in order to assess the attainment of steady state.

- **Part 3 (Single-Dose Food Effect, if conducted):** To compare PF-07202954 exposures following high-fat/high-caloric meal (Test) versus following an overnight fast (Reference) natural log-transformed C_{max}, AUC_{last}, and AUC_{inf} (if data permit) will be analyzed using a mixed effects ANOVA described in Section 5.2. Estimates of the adjusted mean differences (Test-Reference) and the corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

In addition for Part 3 –

- Plasma concentrations of PF-07202954 will be descriptively summarized and plotted by nominal PK sampling time and treatment;

- The plasma PK parameters AUC_{inf}, C_{max}, AUC_{last}, T_{max}, T_{lag}, CL/F, V_z/F, and $t_{½}$ will be summarized descriptively by treatment;

- For AUC_{inf}, C_{max}, and AUC_{last}, box and whisker plots will be presented by treatment and overlaid with geometric means.

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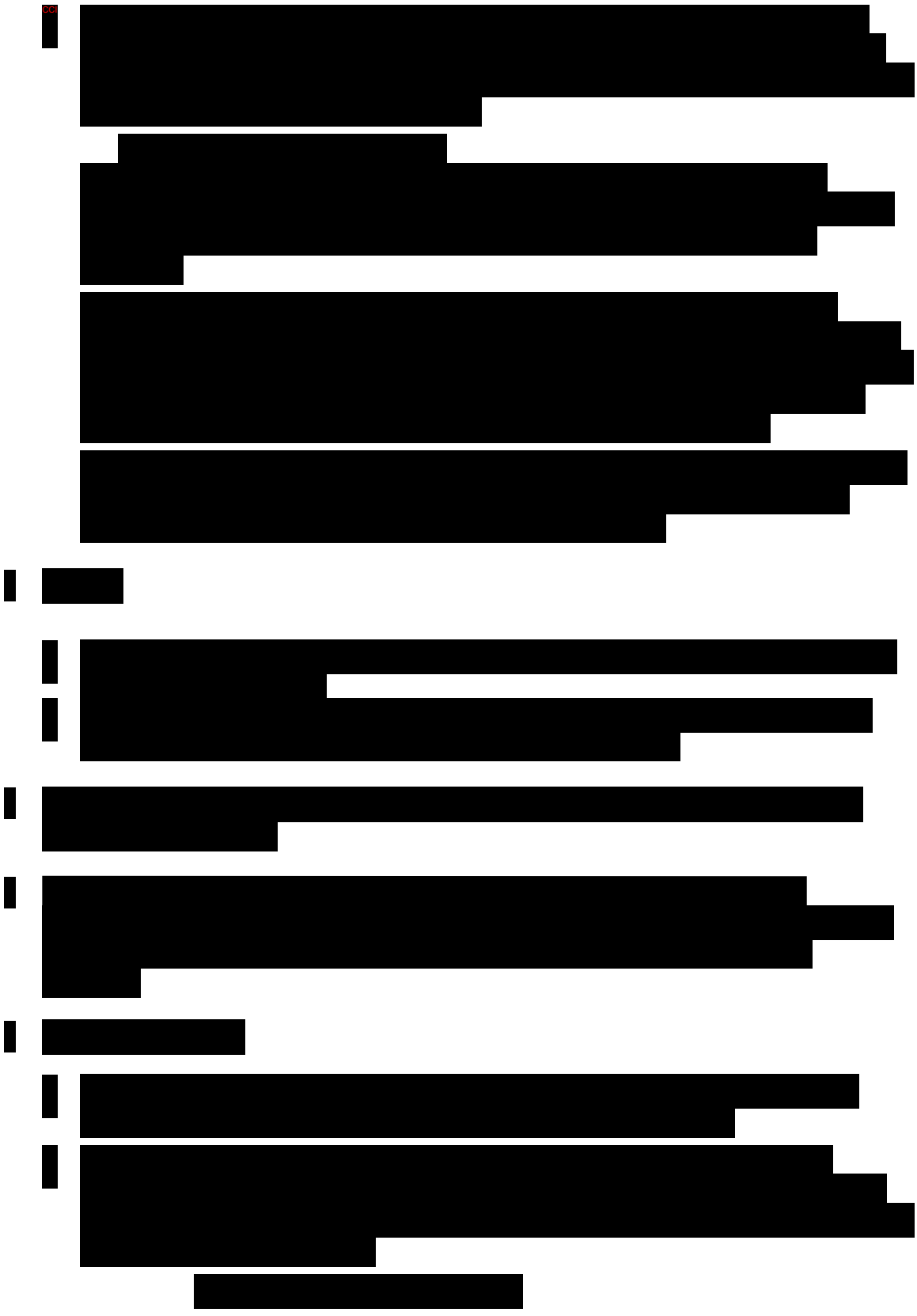

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6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

Data will be reported separately for each part of this 3-part study in accordance with the sponsor's reporting standards.

6.5.1. Baseline Summaries

Demographic data collected at screening will be reported as part of the standard baseline summary tables. A breakdown of demographic data will be provided for age, race, weight, and body mass index.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show end of study participant disposition. The presentation will include counts of participants analyzed for pharmacokinetics, and for safety. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment.

6.5.3. Concomitant Medications and Nondrug Treatments

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

6.5.4. Screening Data

These data will not be recorded in the study database, and therefore will not be listed.

6.6. Safety Summaries and Analyses

No formal analyses are planned for the standard safety data.

The safety endpoints detailed in Section 6.6.5 will be listed and summarized separately for each part of the study and in accordance with sponsor reporting standards based on the safety population (as defined in Section 4, Table 6), with more details provided below.

Medical history and physical examination information, 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. Data collected at screening that are used for

inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted.

6.6.1. Treatment Emergent Adverse Events

Treatment emergent adverse events will be reported in accordance with the sponsor reporting standards.

6.6.2. Laboratory Data

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

6.6.3. Vital Signs

Parts 1 and 2 only

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment and time postdose, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

Mean changes from baseline for supine systolic and diastolic blood pressure and pulse rate will be plotted against time postdoses. On each plot, there will be 1 line for each treatment, all treatments on the same plot including the placebo. Corresponding individual plots of changes from baseline will also be produced for each treatment.

For supine systolic and diastolic blood pressure and pulse rate, the differences between each dose and placebo (dose – placebo) will be summarized (N, mean, 90% CI) and plotted (mean) for each dose and time postdose (including baseline).

Parts 1, 2 and 3 (if conducted)

Maximum absolute values and changes from baseline for vital signs will be summarized descriptively by treatment using categories as defined in Appendix 1. Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Maximum increase or decrease in vital signs will also be summarized; all planned and unplanned postdose timepoints will be included in these summaries.

6.6.4. Electrocardiograms

Parts 1 and 2 only

Absolute values and changes from baseline for the ECG parameters QT interval, HR, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.4.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time postdose. On each plot there will be 1 line for each treatment, all treatments on the same plot including the placebo. Corresponding individual plots of changes from baseline will also be produced for each treatment.

In addition for QTcF, heart rate and QT, the differences between each dose and placebo (dose – placebo) will be summarized and plotted (N, mean, 90% CI) for each dose and timepoint (including baseline).

Changes from baseline in QTcF will be plotted separately against drug concentrations. 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.

In addition, an attempt may 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 may be examined. However, this analysis will not be presented in the CSR.

Parts 1, 2 and 3 (if conducted)

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using categories as defined in Appendix 1 (for QTc these correspond to ICH E14). Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

When more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that timepoint. 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 number of subjects with corrected (QTcF) and uncorrected single post-dose QT values ≥500 msec will be listed.

QTcB, if collected, will be listed only and not summarized.

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7. INTERIM ANALYSES

7.1. Introduction

As guided by observed safety/tolerability, PK, CCI [redacted] in Part 1 and Part 2 of this study, a formal interim analysis may be considered to evaluate potential revision to the currently proposed AUC_{24} PK stopping limit in Part 2 (ie, AUC_{24}=3,680 ng•h/mL). This interim analysis will be used to evaluate whether repeated,

escalating doses of PF-07202954 yielding exposures greater than the currently planned PK stopping limit in Part 2 are attempted. If data are supportive, studying higher exposures will be contingent on a protocol amendment which will undergo the required regulatory and EC/IRB approvals.

As this is a sponsor-open study, a limited number of the sponsor's team members (excluding site staff) may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

If conducted, the objective of the interim analysis will be primarily to evaluate the PK stopping limit in Part 2 so that doses yielding higher exposures can be administered. To enable this PK, standard safety data and the biomarkers of kidney safety from all cohorts in Part 1 and Part 2 up to the date of data snapshot will be extracted and analyzed. The unblinded data will be reviewed by the clnical, statistics and clinical pharmacology leads for this study and their leadership team. In addition, programming team will be unblinded. Participants, investigators and the site staff (except for the site pharmacist) will remain blinded. This is consistent with the sponsor-open design of this study and hence the standard methods of maintaining study blind will be implemented. The data to support interim analysis will be analyzed using the methods described in this SAP.

8. REFERENCES

1. CDISC Safety Rulebook - URL
2. McGill, R., John W. Tukey and W. A. Larsen., (1978), Variations of Box Plots. *American Statistician* 32:12-16
3. Wu, J, Banerjee, A., Jin, B., Menon, S., Martin, S., and Heatherington, A., (2017), Clinical dose-response for a broad set of biological products: A model-based meta-analysis, *Statistical Methods in Medical Research,* Vol. 7, No. 9, 2694-2721.
4. Thomas, N., and Roy, D. (2017). Analysis of clinical dose-response in small-molecule drug development: 2009-2014. *Statistics in Biopharmaceutical Research,* Vol. 9, No. 2, 137-146.
5. Thomas, N., Sweeney, K., and Somayaji, V. (2014). Meta-analysis of clinical dose response in a large drug development portfolio, *Statistics in Biopharmaceutical Research,* Vol. 6, No.4*,* 302-317.
6. FDA Biomarker Qualification Decision and Executive Summary - URL

1. Appendices

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

Bayesian analysis

Categories for QTcF

Categories for Maximum Post-dose QTcF (msec)				
All participants	≤450	450 - ≤480	480 - ≤500	>500
Categories for Maximum Increase from Baseline in QTcF (msec)				
All participants	≤30	30 - ≤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
Standing pulse rate (bpm)	min. <40	max. >140

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

Appendix 2. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
Ae_{tau}	Amount of unchanged drug recovered in urine during dosing interval
Ae_{tau}%	Percent of dose recovered in urine as unchanged drug over dosing interval
ANCOVA	analysis of covariance
ANOVA	Analysis of variance
AUC	area under the curve
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
CCI	[redacted]
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
CCI	[redacted]
AUC_{tau}	area under the concentration-time curve from time 0 to time τ (tau)
$AUEC_{24}$	area under the effect curve over the time of 0-24 hours post dose
BLQ	below the limit of quantitation
BP	blood pressure
CAP™	Controlled attenuation parameter (trademarked by EchoSens®)
C_{av}	average concentrations
CDISC	Clinical Data Interchange Standards Consortium
CFB	Change from baseline
CI	confidence interval
C_{last}	Last quantifiable plasma concentration
CL/F	apparent clearance following oral administration
CL_r	renal clearance
CL	Systemic clearance
CM	Composite measure
C_{max}	maximum observed concentration
CCI	[redacted]
C_{min}	minimum observed concentration
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
%CV	percent coefficient of variation
CYP	cytochrome P450
CCI	[redacted]
E_0	Efficacy at 0 dose level; also treated as placebo effect
EC	ethics committee
ECG	electrocardiogram
ED_{50}	effective dose for 50% of the maximal efficacy
E_{max}	maximum response achievable

Abbreviation	Term
FDA	Food and Drug Administration (United States)
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
GCP	Good Clinical Practice
GM	Geometric mean
GMC	geometric mean concentration
GMR	Geometric mean ratio
HDL-C	high-density lipoprotein cholesterol
CCI	[redacted]
HR	Heart Rate
IA	Interim Analysis
ICH	International Council for Harmonisation
K_{el}	terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
CCI	[redacted]
LDL-C	low-density lipoprotein cholesterol
LLQ	lower limit of quantitation
LS	least-squares
LSM	least-squares mean
MAR	Missing at random
MATE	multidrug and toxin extrusion
max	maximum
min	minimum
MMRM	mixed-effects model with repeated measures
CCI	[redacted]
N/A	not applicable
CCI	[redacted]
NC	Not calculated
ND	Not done
CCI	[redacted]
NS	No sample
CCI	[redacted]
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PO	per oral
PP	per-protocol
PR interval	interval between the start of the electrocardiogram P wave and start of QRS complex, corresponding to time between onset of atrial depolarization and onset of ventricular depolarization
PT	preferred term
PTR	peak-to-trough ratio
QRS	combination of 3 graphical deflections seen on a typical electrocardiogram

Abbreviation	Term
QT	time from electrocardiogram Q wave to end of T wave corresponding to electrical systole
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
R_{ac}	observed accumulation ratio
RR	Response ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
$t_{½}$	terminal elimination half-life
TG	triglyceride(s)
T_{lag}	lag time
T_{max}	time to reach maximum observed concentration
ULN	upper limit of normal
VCTE™	Vibration-controlled transient elastography (trademarked by EchoSens®)
VLDL-C	very low density lipoprotein cholesterol
V_{ss}	steady-state volume of distribution following IV infusion
V_z/F	apparent volume of distribution following oral administration

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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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