Protocol *C2541007*

A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE, 2-PERIOD STUDY IN HEALTHY ADULT MALE PARTICIPANTS TO ASSESS THE EXTENT OF EXCRETION, ABSOLUTE BIOAVAILABILITY, FRACTION ABSORBED, AND PHARMACOKINETICS OF [^{14}C]PF-06865571 USING A ^{14}C-MICROTRACER APPROACH

Statistical Analysis Plan (SAP)

Version: 1.0

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	March 01, 2021	PPD	Not Applicable

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

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

PF-06865571 is a diacylglycerol acyltransferase 2 (DGAT2) inhibitor that is currently being developed for the treatment of nonalcoholic steatohepatitis (NASH) with liver fibrosis.

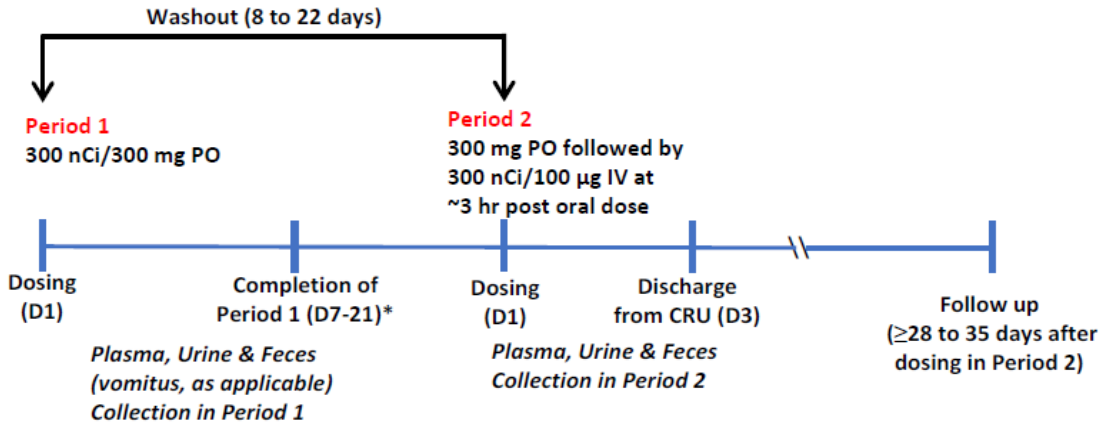
The purpose of this study is to assess the extent of excretion of PF-06865571 as well as the absolute bioavailability, fraction absorbed and pharmacokinetics of PF-06865571 in healthy male participants using a ^{14}C microtracer dose approach.

2.1. Study Design

This study is a Phase 1, open-label, non-randomized, 2-period, fixed-sequence, single-dose study of PF-06865571 in healthy male participants to characterize the ADME properties of [^{14}C]PF-06865571 following oral administration; and to evaluate the absolute oral bioavailability (F) and fraction absorbed (Fa) of PF-06865571 following oral administration of unlabeled PF-06865571 and IV administration of [^{14}C]PF-06865571.

In this study, 6 participants will be enrolled to ensure evaluable data is acquired in at least 4 participants. Each participant will receive 2 regimens (A and B) in Periods 1 and 2, respectively, as outlined in Figure 1. Participants who withdraw from the study may be replaced if the number of evaluable participants is less than 4.

Figure 1. Two Period Fixed Sequence Study Design



** Completion of Period 1 (1 participant at a time) when at least 1 of 3 criteria are met: (1) ≥90% of radioactive dose has been recovered in urine+feces+emesis (if any); (2) <1% of radioactive dose has been recovered in urine+feces during 24H interval over 2 consecutive days; (3) participant has reached Day 21 (in Period 1). At the latest, Period 2, Day -1 would occur on the same day as Period 1, Day 21.*

Regimen A in Period 1*: An oral dose of 300 mg PF-06865571 containing approximately 300 nCi ^{14}C (ie, radiolabeled PF-06865571).*

Regimen B in Period 2*: An oral dose of 300 mg unlabeled PF-06865571 followed at T_{max} by an IV dose of 300 nCi [^{14}C] in 100 µg of PF-06865571 (3 µCi/mg active drug).*

Screening will occur within 42 days of the first dose of the investigational product in Period 1. All participants will provide informed consent and undergo screening evaluations to determine their eligibility.

Eligible participants will be admitted to the CRU on Day -1 of Period 1 and scheduled to remain in the CRU through the completion of Period 2. As such, inpatient stay will be for a total duration of 12 days (minimum) to 25 days (maximum). Each participant will have 1 follow-up phone call that will occur at least 28 days and up to 35 days following the last dose of investigational product to assess for AEs and SAEs.

A participant is considered to have completed the study if he has completed all phases of the study, including the last scheduled procedure as mentioned in the Schedule of Activities in the study protocol.

2.2. Study Objectives

2.2.1. Primary Objectives

- *To characterize the extent of excretion of total radioactivity in urine and feces following administration of a single oral dose of [^{14}C] PF-06865571.*
- *To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of [^{14}C] PF-06865571.*

2.2.2. Secondary Objectives

- *To quantify plasma PK parameters of PF-06865571 and total radioactivity following administration of a single oral dose of [^{14}C] PF-06865571.*
- *To quantify plasma PK parameters of PF-06865571 following administration of a single, IV, microtracer of [^{14}C] PF-06865571.*
- *To determine the absolute oral bioavailability (F) of PF-06865571 following administration of a single oral dose of PF-06865571 compared to a single IV microtracer of [^{14}C] PF-06865571.*
- *To determine the fraction of the dose absorbed (Fa) following administration of a single oral dose of [^{14}C] PF-06865571.*

2.2.3. Tertiary/Exploratory Objectives

- *To characterize cumulative rate of excretion of total radioactivity in urine and feces over time following administration of a single oral dose of [^{14}C] PF-06865571.*

- *To quantify plasma PK parameters of PF-06865571 in plasma following administration of a single oral dose of unlabeled PF-06865571.*

- [redacted]

- *To evaluate the safety and tolerability of PF-06865571, administered as a single oral dose of [^{14}C] PF-06865571 or a single oral dose of PF-06865571 followed by administration of a single IV microtracer of [^{14}C] PF-06865571.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or supporting clinical development.

Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No statistical hypothesis is tested in this study.

4.2. Statistical Decision Rules

No decision rules are required.

5. ANALYSIS SETS

5.1. Evaluable Analysis Set

All participants assigned to study intervention and who take at least 1 dose of study intervention.

5.2. Extent of Excretion Analysis Set

Extent of excretion population is defined as all participants who have received 1 dose of [^{14}C] PF-06865571 and who have evaluable total radioactivity concentration (urinary and fecal) data and who had no protocol deviations or AEs (such as vomiting of the dose, diarrhoea or severe constipation) that may have affected the extent of excretion analysis.

5.3. Pharmacokinetic (PK) Analysis Set

5.3.1. Concentration Analysis Set

- *The PK concentration population for unlabelled PF-06895571 is defined as all participants who receive at least 1 dose of unlabelled PF-06895571 and who have at least 1 measurable concentration of unlabelled PF-06895571.*

- *The PK concentration population for ^{14}C is defined as all participants dosed with [^{14}C] PF-06895571, who have at least one ^{14}C measurement.*

5.3.2. Parameter Analysis Set

The PK parameter analysis population for PF-06895571 is defined as all participants treated who have at least 1 of the PF-06895571 PK parameters of interest. The PK parameter analysis population for ^{14}C analysis is defined as all participants treated who have at least one of the ^{14}C parameters of interest. The PK concentration and PK parameter analysis sets may differ.

5.4. Pharmacodynamic Analysis Set

None.

5.5. Safety Analysis Set

All participants 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.

5.6. Other Analysis Sets

None.

5.7. Treatment Misallocations

This is a nonrandomized study. All participants will receive the same treatment.

5.8. Protocol Deviations

Participants who experience events that may affect their PK profile (eg, lack of compliance with dosing) 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.

5.8.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess participants against the inclusion and exclusion criteria as set out in Sections 5.1 and 5.2 of the protocol.

5.8.2. Deviations Assessed Post-Randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

None.

6.2. Primary Endpoints

- *Total recovery of radioactivity in urine, feces and total excreta (urine + feces) as percentage of total radioactive dose administered.*

- *Metabolic profiling/identification and determination of relative abundance of [^{14}C] PF-06865571 and the metabolites of [^{14}C] PF-06865571 in plasma, urine and feces.*

6.3. Secondary Endpoints

- *Period 1: AUC_{last}, C_{max}, T_{max}, and if data permit, AUC_{inf} and $t_{½}$ to describe single oral dose of:*

  - *Total radioactivity in plasma;*

  - *PF-06865571 in plasma.*

- *[^{14}C]PF-06865571 (Period 2): AUC_{last}, C_{max}, T_{max}, and if data permit, $t_{½}$, AUC_{inf}, CL and V_{ss}.*

- *Plasma AUC_{inf} of oral unlabeled PF-06865571 and IV microtracer of [^{14}C] PF-06865571 in Period 2 only.*

- *Total urinary radioactivity following oral administration of [^{14}C] PF-06865571 in Period 1 and IV microtracer administration of [^{14}C] PF-06865571 in Period 2.*

6.4. Tertiary/Exploratory Endpoints

- *Cumulative recovery of radioactivity in urine and feces, and total excreta (urine + feces) over time as a percentage of total radioactive dose administered.*

- *PF-06865571 plasma (Period 2): AUC_{last}, C_{max}, T_{max}, and if data permit, $t_{½}$, AUC_{inf}, CL/F, V_z/F.*

[redacted]

6.5. Safety Endpoints

An adverse event is considered a treatment emergent if the event started during the effective duration of treatment.

Events that occur in a non-treatment period (for example, Washout or Follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events;*
- *laboratory data.*

6.6. Other Endpoints

6.6.1. PK Endpoints

6.6.1.1. Plasma PK Analysis

Blood samples will be collected according to the Schedule of Activities given in the protocol.

Blood will be analyzed for concentrations of total radioactivity. Plasma will be analyzed for concentrations of PF-06865571 and (if possible) its major metabolite(s).

The following parameters will be determined using standard non-compartmental methods and will be listed and summarized descriptively:

Table 1. Noncompartmental PK Parameters of Plasma

		After oral dose of [^{14}C] PF-06865571 (Period 1)		After oral dose of PF-06865571 (Period 2)	After IV dose of [^{14}C] PF-06865571 (Period 2)
Parameter	**Analysis Scale**	**PF-06865571**	**Total ^{14}C**	**PF-06865571**	**[^{14}C] PF-06865571**
AUC_{last}	ln	D	D	D	D
AUC_{last}(dn)	ln	D	D	D	D
AUC_{inf}*	ln	D	D	D	D
AUC_{inf}(dn)	ln	D	D	D	D
C_{max}	ln	D	D	D	D
C_{max}(dn)	ln	D	D	D	D
T_{max}	R	D	D	D	D
$t_{1/2}$*	R	D	D	D	D
CL/F* (oral)	ln	D	D	D	NA
CL* (IV)	ln	NA	NA	NA	D
V_z/F* (oral)	ln	D	D	D	NA
V_{ss}* (IV)	ln	NA	NA	NA	D

[redacted]

[redacted]

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits, dn=dose normalized to a 1 mg dose, IV=intravenous, NA=not applicable.

Additionally, T_{last} will be provided as a supportive parameter for AUC_{last}. T_{last} will be listed only and not summarized.

6.6.2. PD Endpoints

None.

6.7. Covariates

None.

7. HANDLING OF MISSING VALUES

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

7.1. 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).

7.2. 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.

7.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters. In the event that actual time is missing, nominal time may be used.

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 treatment group/analyte with ≥3 evaluable measurements.

For statistical analyses (ie, mixed effect 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, or not completing the meal before dosing), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Precision of the estimate of PK parameters will be determined by constructing 90% confidence intervals around the estimated difference between the Test and Reference treatments using a mixed effects model based on natural log transformed data. The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger degrees of freedom algorithm.

8.2. Statistical Analyses

8.2.1. Extent of Excretion (Period 1)

Radioactivity excreted in urine and/or feces will be reported as the percentage of the administered radioactivity excreted at each time interval, cumulatively through that interval and the total percent of dose recovered in urine and/or feces.

Percent recovery and cumulative recovery of total radioactivity in urine, feces and emesis (if any) will be determined based on total administered dose.

Individual participant and median data profiles will be graphically presented for the cumulative recovery of radioactivity in emesis, urine, feces and their combination. The total recovery of radioactivity in urine, feces and their combination will be listed and summarized using descriptive statistics. Where possible, the rate of excretion of radioactivity will be estimated.

Results of the extent of excretion analysis (ie, radioactivity in plasma, urine, and feces, and emesis if observed) will be detailed in a separate report provided and will be summarized within the Clinical Study Report (CSR).

8.2.2. Metabolic Profiling/Identification (Period 1)

Plasma, urine and fecal samples will be analyzed for metabolites of PF-06865571. Major metabolites of PF-06865571 in plasma, urine, and feces following oral dose of [^{14}C] PF-06865571 will be identified if possible. Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the CSR.

8.2.3. Pharmacokinetic Analysis

The PK parameters detailed in Section 6.3 will be listed and summarized for participants in the appropriate analysis sets (as defined in Section 5.3). Missing values will be handled as detailed in Section 7.

8.2.3.1. Plasma

The PF-06865571 PK parameters following a single dose administration of unlabeled PF-06865571 (oral) and microtracer dose of [^{14}C] PF-06865571 (oral and IV) will be derived, where appropriate, from the concentration-time profiles as outlined below:

- *Parameters for total ^{14}C (^{14}C oral microtracer) will be derived for Period 1 only;*
- *Parameters for PF-06865571 after oral doses of ^{14}C oral microtracer and unlabeled PF-06865571 for Periods 1 and 2, respectively and for [^{14}C] PF-06865571 after ^{14}C IV microtracer for Period 2 will be derived.*

Plasma PK parameters above will be listed and summarized descriptively by analyte (total ^{14}C, unlabeled PF-06865571, and [^{14}C] PF-06865571) and treatment, as applicable.

8.2.3.2. Absolute Oral Bioavailability (F)

F will be estimated as the ratio of adjusted geometric means of dose-normalized AUC_{inf} (if data permit, otherwise AUC_{last}) for oral unlabeled PF-06865571 and IV labeled.

^{14}C-PF-06865571 in plasma (from Period 2 only) which is equivalent to the following equation:

$$F = [\text{PF-06865571\_}AUC_{po} / [^{14}\text{C}]\ \text{PF-06865571\_}AUC_{iv}] \times [[^{14}\text{C}]\ \text{PF-06865571\_}Dose_{iv} / \text{PF-06865571\_}Dose_{po}]$$

Geometric mean ratio and 90% confidence interval: Natural log transformed AUC_{inf}(dn) (if data permit) and AUC_{last}(dn) from Period 2 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted (least squares) mean differences (Test-Reference) and the corresponding 90% CI 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% CI for the ratio. IV [^{14}C] PF-06865571 is the Reference formulation and unlabeled oral PF-06865571 is the Test formulation.

8.2.3.3. Fraction Absorbed (Fa)

8.2.3.3.1. Urine Parameters

Following urine parameters will be calculated following single dose administration of a microtracer dose of [^{14}C] PF-06865571 (oral and IV administration). Residual ^{14}C levels from Period 1 will be accounted for using an appropriate method, based on AMS principles and methodology.

Parameter	Definition	Method of Determination
Total ^{14}C_Urine_PO	*Total radioactivity excreted into the urine postdose following oral administration of [^{14}C]PF-06865571 microtracer dose*	*Sum of [^{14}C urine concentration × sample volume] for each collection interval*
Total ^{14}C_Urine_IV	*Total radioactivity excreted into the urine following IV administration of [^{14}C]PF-06865571 microtracer dose*	*Sum of [^{14}C urine concentration × sample volume] for each collection interval*
%^{14}C_Urine_PO	*Percent of the radioactive dose administered that is excreted in the urine following oral administration*	*Total ^{14}C_Urine_PO/^{14}C Dosepo × 100 Where ^{14}C Dosepo is the dose of ^{14}C following oral administration of [^{14}C]PF-06865571*
%^{14}C_Urine_IV	*Percent of the radioactive dose administered that is excreted in the urine following IV administration*	*Total ^{14}C _Urine_IV/^{14}C Doseiv × 100 Where ^{14}C Doseiv is the dose of ^{14}C following IV administration of [^{14}C]PF-06865571*

Total urine ^{14}C amounts, percent ^{14}C dose will be listed by treatment (oral in Period 1 and IV in Period 2) and summarized using descriptive statistics.

8.2.3.3.2. Calculation of Fa

Fa will be estimated as the ratio of the adjusted geometric means of % of administered radioactive dose excreted into the urine following oral and IV administration of [^{14}C]PF-06865571 microtracer dose over the same collection time (up to 48 hours post dose) in Periods 1 and 2, respectively:

$$Fa = [\%\ ^{14}C\_Urine\_PO / \%\ ^{14}C\_Urine\_IV]$$

Geometric mean ratio and 90% confidence interval: Natural log transformed % Total ^{14}C in Urine from Period 1 and Period 2 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted (least squares) mean differences (Test-Reference) and the corresponding 90% CI 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% CI for the ratio. Total ^{14}C_Urine_IV is the Reference formulation and Total ^{14}C_Urine_PO is the Test formulation.

Theoretically Fa would be expected to be greater than F. In the event that F is estimated to be greater than Fa, the greater of the 2 values will be used to represent the fraction of PF-06865571 absorbed. PF-06865571 will be considered highly permeable if either F or Fa is greater than 0.85.

PK parameters will be summarized by treatment and analyte as specified in Table 2.

Table 2. PK Parameters to be Summarized Descriptively

Matrix	Parameter	Summary Statistics
Plasma	AUC_{last}, AUC_{last}(dn), AUC_{inf}, AUC_{inf}(dn), C_{max}, C_{max}(dn), F, [CL/F (oral) or CL (IV)] and [V_Z/F (oral) or V_{ss} (IV)]	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
Plasma	T_{max}	N, median, minimum, maximum.
Plasma	$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.
Urine	Total ^{14}C Urine PO, Total ^{14}C Urine IV, % ^{14}C Urine PO, % ^{14}C Urine IV, Fa	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

Box and whisker plots for individual participant parameters (AUC_{inf}(dn), AUC_{last}(dn), C_{max}(dn), % ^{14}C urine PO, and % ^{14}C urine IV) be presented and overlaid with geometric means.

Supporting data from the estimation of $t_{½}$, and AUC_{inf} will be listed by analyte: 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.

Presentations for PK (plasma, where possible) concentrations by analyte will include:

- A listing of all concentrations sorted by participant id and nominal time postdose for each analyte, route of administration and treatment, separately. The listing of concentrations will include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by nominal time postdose (produced separately for each analyte), 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.

- A plot (on both linear and semi-log scales) of median PK and radioactivity concentrations against nominal time postdose (based on the summary of concentrations by time postdose), where the median concentration-time profiles for plasma PF-06865571 PK (Period 1), and plasma radioactivity (Period 1) will be presented together on the same plot.

- A plot (on both linear and semi-log scales) of median PK and radioactivity concentrations against nominal time postdose (based on the summary of concentrations by time postdose), where the median concentration-time profiles for plasma PF-06865571 PK (Period 2), and plasma [^{14}C] PF-06865571 (Period 2) will be presented together on the same plot where both have been dose-normalized (by oral and IV dose, respectively). The dose-normalization will be calculated by programming using raw concentrations and the actual doses administered.

- Plots (on both linear and semi-log scales) of individual concentrations against actual time postdose by participant. Concentration time plots for analytes PF-06865571 (Period 1) and total radioactivity (Period 1) will be presented together on the same plot. In a separate figure, the analytes PF-06865571 (Period 2) and [^{14}C]PF-06865571 (Period 2), where both have been dose-normalized (by programming using raw concentrations and the actual doses administered), will be presented together on the same plot.

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.

8.3. Safety Analysis

A set of summary tables will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-06865571.

8.3.1. Treatment and Disposition of Participants

Participant evaluation groups will show end of study participant disposition and will show which participants were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for participant discontinuation(s).

Data will be reported in accordance with the sponsor reporting standards.

8.3.2. Demographic and Clinical Examination Data

A break-down of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized as 'All Participants' in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Participant discontinuations, and/or temporary discontinuations due to adverse events will be detailed and summarized.

Data will be reported in accordance with the sponsor reporting standards.

8.3.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

8.3.5. Laboratory Data

The baseline measurement is the last predose measurement taken prior Period 1, Day 1 dose.

Laboratory data will be summarized and listed in accordance with the sponsor reporting standards.

8.3.6. Vital Signs Data

Vital Signs data will be databased and available upon request.

8.3.7. ECG Data

ECG data will be databased and available upon request.

8.3.8. Other Safety Data

None.

8.3.9. Concomitant Treatments

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

8.3.10. Screening and Other Special Purpose Data

All the screening data will not be brought in-house, and therefore will not be listed.

CCI [redacted]

8.3.12. Banked Bio-specimen data

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9. REFERENCES

None.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

An example of the PROC MIXED code for Plasma data analysis is provided below:

```
proc mixed data=tab.pk;
        class trt participant;
        model l&var= trt/ ddfm=KR;
        random participant /participant=participant;
        lsmeans trt;
        estimate 'Test vs Reference' trt -1  1  /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;


/* Letter assignments for treatments (trt) within the estimate statement above are as follows;

For F:

A = Reference = IV 14C-PF-06865571
B = Test      = oral PF-06865571

For Fa:

A = Reference = Total 14C_Urine_IV
B = Test      = Total 14C_Urine_PO

*/;
```