Protocol C3421038

A PHASE 1, OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETIC INTERACTIONS BETWEEN PF-06882961 AND PF-06865571 IN HEALTHY ADULT PARTICIPANTS (PART A) AND OVERWEIGHT ADULTS OR ADULTS WITH OBESITY WHO ARE OTHERWISE HEALTHY (PART B)

Statistical Analysis Plan
(SAP)

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol / Amendment	Rationale	Specific Changes
1 07-Apr-2021	Protocol Amendment 1 12-Mar-2021	N/A	N/A
2 07-Jul-2021	Protocol Amendment 2 03-Jun-2021	Preliminary draft data from study C3421007 indicate that a decrease in exposure of midazolam are observed when co-administered with PF-06882961. To investigate the mechanism of this interaction, assessment of plasma 4-β-hydroxycholesterol/cholesterol, an endogenous probe for CYP3A induction, is being added in Part B. In vitro studies indicate PF-06882961 may inhibit OATP1B1 at dose(s) evaluated in this study. Therefore, to evaluate this potential effect of PF-06882961, measurement of plasma CP-I, an endogenous probe for OATP1B activity, is being added in Part B.	Section 2.1 modified to introduce endogeneous endpoints, Sections 3.3, 5.3.4, 6.3.5 and 6.3.6 created to specify the analyses and reporting of the endogeneous endpoints. Appendix 4 modified to introduce acronyms related to the enedgoneous endpoints

2. INTRODUCTION

This study will evaluate the PK interactions between PF-06882961 and PF-06865571 in healthy adult participants (Part A) and overweight adults or adults with obesity who are otherwise healthy (Part B).

This statistical analysis plan (SAP) provides the *detailed methodology for summary and statistical analyses of the data collected* in Study C3421038. 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

Objectives	Endpoints
Part A	
Primary:	***Primary:***
To evaluate the effects of PF-06865571 on the single-dose pharmacokinetics of PF-06882961 in healthy adult participants.	*PF-06882961 plasma pharmacokinetic parameters: C_{max} and AUC_{24}.*
Secondary:	***Secondary:***
To evaluate the safety and tolerability of PF-06882961 alone and in combination with PF-06886571 when administered to healthy adult participants.	*Assessment of treatment-emergent adverse events, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters during the entire study.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
To evaluate the effects of PF-06865571 on additional pharmacokinetic parameters of PF-06882961 in healthy adult participants.	*Additional PF-06882961 plasma pharmacokinetic parameters: T_{max}.*
Part B	
Primary:	***Primary:***
To evaluate the effects of PF-06882961 on the single-dose pharmacokinetics of PF-06865571 in overweight adults or adults with obesity who are otherwise healthy. *To evaluate the effects of PF-06865571 on the multiple-dose pharmacokinetics of PF-06882961 in overweight adults or adults with obesity who are otherwise healthy.*	*PF-06865571 plasma pharmacokinetic parameters on Day 1 and Day 47: C_{max}, AUC_{last}, and $AUC_{inf,}$ as data permits.* *PF-06882961 plasma pharmacokinetic parameters on Day 46 and Day 61: C_{max} and AUC_{12}.*
Secondary:	***Secondary:***
To evaluate the safety and tolerability of PF-06882961 and PF-06865571 when administered separately and in combination in overweight adults or adults with obesity who are otherwise healthy.	*Assessment of treatment-emergent adverse events, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters during the entire study.* *Assessment of mental health as determined by C-SSRS and PHQ-9 in Part B of this study.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
To evaluate the effects of PF-06882961 on additional pharmacokinetic parameters of PF-06865571 in overweight adults or adults with obesity who are otherwise healthy.	*Additional PF-06865571 plasma pharmacokinetic parameters on Day 1 and Day 47: T_{max}, CL/F, V_z/F, and $t_{½}$, as data permits.*

To evaluate the effects of PF-06865571 on additional pharmacokinetic parameters of PF-06882961 in overweight adults or adults with obesity who are otherwise healthy.	*Additional PF-06882961 plasma pharmacokinetic parameters on Day 46 and Day 61: T_{max} and CL/F.*
CCI	
To evaluate the effects of PF-06882961 on the multiple-dose pharmacokinetics of PF-06865571 in overweight adults or adults with obesity who are otherwise healthy.	*PF-06865571 plasma pharmacokinetic parameters on Day 61: C_{max}, T_{max}, and AUC_{12}.*
To evaluate the effects of multiple doses of PF-06882961 on CYP3A induction in overweight adults or adults with obesity who are otherwise healthy.	*Morning pre-dose 4-β-hydroxycholesterol/cholesterol plasma ratio on Days 1, 19, 31, and 47.*
To evaluate the effect of multiple doses of PF-06882961 on coproporphyrins I in overweight adults or adults with obesity who are otherwise healthy.	*CP-I parameters on Days 30 and 46: AUC_{12} and C_{max}.*

2.1.1. Primary Estimand(s)

Not applicable

2.1.2. Secondary Estimand(s)

Not applicable

2.1.3. Additional Estimand(s)

Not applicable

2.2. Study Design

This study will be conducted in 2 parts.
Part A *is an open-label, two-period, two-sequence, crossover cohort investigating the potential effect of PF-06865571 on the PK of PF-06882961 in healthy adult participants.*
Part B *is an open-label, fixed-sequence cohort to evaluating the effect of PF-06882961 on the PK of PF-06865571, as well as the effect of PF-06865571 on the PK of PF-06882961 in overweight adults or adults with obesity who are otherwise healthy. The effect of PF-06882961 on PF-06865571 PK will be evaluated at steady-state* at a dose of up to 200 mg BID *of PF-06882961. Then, PF-06882961 and PF-06865571 will be coadministered for approximately 2 weeks for further evaluation of PK interactions and to generate additional safety and tolerability data on the combination.*

A cohort of approximately 8 participants will be enrolled in Part A. Approximately 16 participants will be enrolled in Part B such that approximately 12 evaluable participants complete Part B.

2.2.1. *Treatment Scheme for Part A*

	Period 1	***Washout****	***Period 2***
Sequence 1 *(n=4)*	*Treatment A: 20 mg PF-06882961 single dose*	*Washout of at least 3 days**	*Treatment B: 20 mg PF-06882961 single dose plus 300 mg PF-06865571 single dose*
Sequence 2 *(n=4)*	*Treatment B: 20 mg PF-06882961 single dose plus 300 mg PF-06865571 single dose*	*Washout of at least 3 days**	*Treatment A: 20 mg PF-06882961 single dose*
**Each participant is planned to undergo 2 treatment periods with a washout interval between periods of at least 3 days following the final dose of study intervention administered in Period 1.*			

2.2.2. *Treatment Scheme for Part B*

	Period 1	***Period 2***	***Period 3***	***Period 4***
	Days 1-2	***Days 3-46***	***Days 47-48***	***Days 49-62***
PF-06865571 (DGAT2) Dose	*300 mg single dose on Day 1 only[a]*	*N/A*	*300 mg single dose on Day 47 only[a]*	*300 mg BID on Days 49-61[a]*
PF-06882961 (GLP-1) Dose	*N/A*	*10 mg BID titrated to 200 mg BID[b,c]*	*200 mg BID[c]*	*200 mg BID on Days 49-61[b,c]*

a. *Dense PK sampling for measurement of PF-06865571 plasma concentrations on Day 1 (reference), Day 47 (test), and Day 61 (summary statistics only).*

b. *Dense PK sampling for measurement of PF-06882961 plasma concentrations on Day 46 (reference) and Day 61 (test).*

c. *Doses of PF-06882961 may be reduced based on PK results of Part A of this study and safety and tolerability results of Study C3421007.*

In all study parts (Part A and Part B), participants will remain on-site (inpatient study) for the duration of the dosing period, followed by one follow-up outpatient visit. A further follow-up contact with participants will be conducted at least 28 days and up to 35 days after the last administration of IP; this contact may be done via a phone call.

The study will be conducted in the US.

Participants who discontinue prior to completion of the study may be replaced, at the discretion of the principal investigator (PI) and sponsor (applicable to part A only).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Blood samples for PK analysis of PF-06865571, PF-06882961 CCI [redacted] will be taken according to the Schedule of Activities (SoA) given in the protocol.

In Part A, plasma PF-06882961 PK parameters following single administration of PF-06882961 will be derived using standard noncompartmental methods, as data permit, for each treatment, from the concentration time profiles as follows:

Table 2. Part A – Plasma PK Parameters for PF-06882961

Parameter	Analysis Scale	PF-06882961
AUC_{24}	ln	D
C_{max}	ln	D
T_{max}	R	D

Key: D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed)

In Part B, plasma PF-06865571, PF-06882961, CCI [redacted] PK parameters following single administration of PF-06865571 and PF-06882961 or multiple-dose of PF-06882961 will be derived using standard noncompartmental methods, as data permit, for each treatment and day (as appropriate), from the concentration time profiles as follows:

Table 3. Part B – Plasma PK Parameters for PF-06882961, CCI [redacted] and PF-06865571

Parameter	Compound CCI [redacted]	Days	Analysis Scale	Reporting
AUC_{last}	PF-06865571	1 and 47	ln	D
AUC_{inf}*	PF-06865571	1 and 47	ln	D
AUC_{12}	PF-06865571	61	ln	D
	PF-06882961 CCI [redacted]	46 and 61		
C_{max}	PF-06865571	1, 47, and 61	ln	D
	PF-06882961 CCI [redacted]	46 and 61		
T_{max}	PF-06865571	1, 47, and 61	R	D
	PF-06882961 CCI [redacted]	46 and 61		

$t_{1/2}$*	PF-06865571	1 and 47	R	D
CL/F*	PF-06865571	1 and 47	ln	D
	PF-06882961	46 and 61		
Vz/F*	PF-06865571	1 and 47	ln	D
CCI				

Key: D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits

3.2. Secondary Endpoint(s)

3.2.1. Safety Endpoints

- *Assessment of treatment-emergent adverse events, clinical laboratory abnormalities, vital signs, body weight and ECG parameters during the entire study.*

Any events occurring following start of study intervention (i.e. treatment) will be counted as treatment emergent.

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

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

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

- adverse events,
- laboratory data,
- vital signs data,
- body weight
- ECG results.

For laboratory, vital signs and ECG data there will be two separate definitions for baseline that will be calculated depending on the study part:

i) For Part A, using the last pre-dose measurement within each respective treatment Period
ii) For Part B, using a fixed baseline of the last pre-dose measurement in Period 1.

Change from baseline will therefore be calculated twice for each relevant safety endpoint using (i) and (ii) above.

Definitions of baseline body weight for exploratory safety analyses are described in Section 3.2.3.

3.2.2. Assessment of Mental Health (Part B Only)

- *Assessment of mental health as determined by C-SSRS and PHQ-9 during the entire study.*

3.2.2.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a validated tool to evaluate suicidal ideation and behavior. Data relevant to the assessment of suicidality will be mapped to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes as given in Appendix 5.

Baseline is defined as the last pre-dose measurement in Period 1. For this endpoint the screening visit will be labelled as 'Lifetime' in tables and the recent history (i.e. past 12 months) will also be reported separately.

3.2.2.2. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a 9 item self-report scale for the assessment of depressive symptoms. The PHQ-9 will be completed by participants and reviewed by site staff at the pre-defined time points outlined in the SoA for Part B.

Baseline is defined as the last pre-dose measurement in Period 1 Day 1.

3.2.3. Other Safety Endpoints (Part B only)

- Change from baseline in PT/INR/aPTT, TBA, HbA1c, body weight, lipids, TSH, Free T4, calcitonin, amylase, and lipase at all post-dose time points as outlined in the SoA for Part B.

Baseline is defined as the last pre-dose measurement in Period 1 Day 1.

3.3. Tertiary Endpoint(s)

In Part B, plasma samples for analysis of 4-β-hydroxycholesterol/cholesterol ratio and CP-I concentrations will be taken according to the Schedule of A.

Plasma CP-I parameters will be derived using standard noncompartmental methods, as data permit, for each treatment and day (as appropriate), from the concentration time profiles as follows:

Table 4. Part B – Plasma CP-I Parameters

Parameter	Marker	Days	Analysis Scale	Reporting
AUC_{12}	CP-I	30 and 46	ln	D
C_{max}	CP-I	30 and 46	ln	D
Key: D=displayed with descriptive statistics, ln=natural-log transformed				

3.4. Baseline Variables

Baseline for all parameters discussed in Section 5 and 6 will be defined as the values assessed on as the closest measurement before dosing (ie pre-dose on Day 1 0H).

When three assessements are performed at baseline, the baseline will be the average of the three values (eg Vital Signs).

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 releasing the database and classifications will be documented per standard operating procedures.

All analyses will be performed on an "as-treated" basis and will not include data from participants who are randomized but not treated. If a participant takes a treatment that is not consistent with the treatment they are randomized to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, PK and PD analyses, where applicable.

Participants who experience events that may affect their PK profile (eg vomiting) may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations (eg medication errors) will be compiled and reviewed to identify major and minor deviations prior to database closure.

Population	Description
Enrolled	*All participants who sign the ICD.*
Randomly assigned to investigational product	*All participants randomly assigned to investigational product regardless of whether or not the investigational product was administered.*

Population	Description
Evaluable	*All participants randomly assigned to investigational product and who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.*
Safety	*All participants randomly assigned to investigational product and who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.*
PF-06865571 *PK Concentration Set*	*The* PF-06865571 *PK concentration population is defined as all randomized participants who received at least 1 dose of* PF-06865571 *and in whom at least 1 plasma concentration value is reported.*
PF-06865571 *PK Parameter Set*	*The* PF-06865571 *PK parameter population is defined as all randomized participants who received at least 1 dose of* PF-06865571 *and in whom at least 1 parameter value is reported.*
PF-06882961 PK Concentration Set	The PF-06882961 concentration population is defined as all randomized participants who received at least 1 dose of PF-06882961 and in whom at least 1 plasma concentration value is reported.
PF-06882961 PK Parameter Set	The PF-06882961 PK parameter population is defined as all randomized participants who received at least 1 dose of PF-06882961 and in whom at least 1 parameter value is reported.
Endogenous biomarker Concentration Set	The endogenous biomarker concentration population is defined as all randomized participants who received at least 1 dose of PF-06882961 and in whom at least 1 plasma concentration (4-β-hydroxycholesterol and cholesterol or CP-I) value is reported.
Endogenous biomarker Parameter Set	The endogenous biomarker parameter population is defined as all randomized participants who received at least 1 dose of PF-06882961 and in whom at least 1 CP-I or 4-β-hydroxycholesterol/cholesterol parameter value is reported.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Not applicable

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

Not applicable

5.2.2. Analyses for Continuous Endpoints

Continuous endpoints and relevant safety endpoints will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values.

5.2.3. Analyses for Categorical Endpoints

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

5.3. Methods to Manage Missing Data

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

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

5.3.1. Pharmacokinetic Concentrations Below the Limit of Quantification

In all PK data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. In listings BLQ values will be reported as "<LLOQ", where LLOQ will be replaced with the value for the lower limit of quantification.

5.3.2. Deviations, Missing Concentrations and Anomalous Values

In PK 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/clinical team.

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

Participants who experience events that may affect their PK profile (e.g. lack of compliance with dosing or vomiting) may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.3.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

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.

If a participant receives a dose that was not assigned based on the randomized titration scheme (for example due to a down-titration), the PK data from that Day will not be included in the calculation of summary statistics but will be included in listings.

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.

5.3.4. 4-β-hydroxycholesterol, cholesterol and Coproporphyrins I Concentrations and Parameters

Rules described in Section 5.3.1, and Section 5.3.2 will be used to manage concentrations below limit of quantification, deviations, missing concentrations and anomalous value for the markers of CYP3-A induction (ie 4-β-hydroxycholesterol/cholesterol ratio), and OATP1B1 Activity (ie coproporphyrins I).

Rules described in Section 5.3.3 will apply to derive parameters for Coproporphyrins I (CP-I) and 4-β-hydroxycholesterol/cholesterol ratio.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. PF-06882961 PK Parameters

Applicable to Parts A, and B – Analyses reported for each part separately.

- Estimand strategy: Not applicable
- Analysis set: PF-06882961 Concentration and Pharmacokinetic Parameter Set

To assess the pharmacokinetics of PF-06882961 in Part A and Part B CCI [redacted] CCI [redacted] the PK parameters detailed in Section 3.1 will be listed and summarized for participants in the PK analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3 along with handling of values where participants received a dose that was not assigned based on the titration scheme). Each PK parameter will be summarized by treatment (eg differentiating different doses and dosing frequencies as required), Study Part and Study Day/Period (as appropriate).

The parameters will include the set of summary statistics as specified in the table below:

Table 5. PF-06882961 CCI [redacted] PK Parameters to be Summarized Descriptively per Day

Part	Parameter	Days	Summary Statistics
A	AUC_{24}, C_{max}	-	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
	T_{max}	-	N, median, minimum, maximum.
B	AUC_{12}, C_{max}, CCI [redacted] CL/F*	46 and 61	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
	T_{max}	46 and 61	N, median, minimum, maximum.

* if data permits

CCI [redacted]

There will be one summary table presenting all PK parameters. The treatment subheading will include the study part, analyte, dose information and day (Day 46 or Day 61). As per Section 5.3.3, data collected on days that participants received anything other than the assigned dose based on the titration scheme will only be listed and not summarized as part of the summary table.

The following plots will be presented:

- Box and whisker plots for individual PK parameters of PF-06882961 (AUC_{24}, and C_{max}) will be presented by treatment and overlaid with geometric means for Part A.
- Box and whisker plots for individual PK parameters of PF-06882961 (AUC_{12}, C_{max}) will be presented by treatment and overlaid with geometric means for Part B.

Presentations for PF-06882961 CCI [redacted] concentrations will include:

- a listing of all concentrations sorted by participant ID, treatment, and matrix and nominal time postdose. 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 treatment, and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- median concentration time plots (on both linear and semi-log scales) against nominal time post-dose by treatment period. One plot for each scale will be presented which will include the different PF-06882961 treatment periods in the same plot.

- mean concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by treatment period. One plot for each scale will be presented which will include the different PF-06882961 treatment periods in the same plot.

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

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-06882961 concentration is quantifiable in the plasma.

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.

6.1.1.1. Effects of PF-06865571 on Single Dose PF-06882961 PK Parameters (Part A)

Natural log-transformed C_{max} and AUC_{24} of PF-06882961 administered alone or co-administered with PF-06865571 will be analyzed using a mixed effect model with treatment, sequence, and period as a fixed effects and participant embedded in sequence as a random effect. The Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. *Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the models. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. The reference treatment will be "PF-06882961 20 mg" administered alone, whereas the test treatment will be "PF-06882961 20 mg plus PF-06865571 300 mg BID"*

6.1.1.2. Effect of PF-06865571 on the Multi-Dose of PF-06882961 PK Parameters (Part B)

To analyze the effects of PF-06865571 on multi-dose PF-06882961 PK parameters, *natural log-transformed AUC_{12} and C_{max} of PF-06882961 200 mg BID administered alone* (Period 2 – Day 46) *or co-administered with PF-06865571 300 mg BID* (Period 4 – Day 61) *will be analyzed* using a mixed effect model including treatment as fixed effects and participant as random effect. The Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the models.The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. *The test treatment will be "PF-06865571 300 mg BID plus PF-06882961 200 mg BID" (Period 4 –* Day 61*), which will be reported separately in comparison to the reference treatment of "PF-06882961 200 mg BID administered alone" (Period 2 –* Day 46*).*

6.1.2. PF-06865571 PK Parameters

Applicable to Part B only.

- Estimand strategy: Not applicable
- Analysis set: PF-06865571 Concentration and Pharmacokinetic Parameter Set

To assess the pharmacokinetics of PF-06865571, the PK parameters detailed in Section 3.1 will be listed and summarized for participants in the PK analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3 along with handling of values where participants received a dose that was not assigned based on the titration scheme). Each PK parameter will be summarized by treatment (eg differentiating different doses and dosing frequencies as required), and Study Day as applicable.

The parameters will include the set of summary statistics as specified in the table below:

Table 6. PF-06865571 PK Parameters to be Summarized Descriptively

Parameter	Days	Summary Statistics
AUC_{last}, AUC_{inf}*, CL/F*, Vz/F*	1 and 47	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	1, 47 and 61	N, median, minimum, maximum.
$t_{1/2}$*	1, and 47	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

C_{max}	1, 47 and 61	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
AUC_{12}	61	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

* if data permits

There will be one summary table presenting all PK parameters. The treatment subheading will include the analyte, dose information and day (Day 1, Day 47 or Day 61). As per Section 5.3.3, data collected on days that participants received anything other than the assigned dose based on the titration scheme will only be listed and not summarized as part of the summary table.

The following plots will be presented:

- Box and whisker plots for individual PK parameters of PF-06865571 (AUC_{last}, AUC_{inf}*, and C_{max}) will be presented by treatment and overlaid with geometric means.

Presentations for PF-06865571 concentrations will include:

- a listing of all concentrations sorted by participant ID, treatment, and matrix and nominal time postdose. 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 treatment, and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- median concentration time plots (on both linear and semi-log scales) against nominal time post-dose by treatment period. One plot for each scale will be presented which will include the different PF-06865571 treatment periods in the same plot.

- mean concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by treatment period. One plot for each scale will be presented which will include the different PF-06865571 treatment periods in the same plot.

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

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-06865571 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.

6.1.2.1. Effect of PF-06882961 on Single Dose PF-06865571 PK Parameters (Part B)

To analyze the effects of PF-06882961 on single-dose PF-06865571 PK parameters, *natural log-transformed C_{max}, AUC_{last}, and AUC_{inf} (as data permit) of PF-06865571 300 mg BID administered alone or co-administered with PF-06882961 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect.* The Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. *Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the models. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. The test treatment will be "PF-06865571 300 mg plus PF-06882961 200 mg BID" (Period 3 –* Day 47*), which will be reported separately in comparison to the reference treatment of "PF-06865571 300 mg" (Period 1 –* Day 1*).*

[redacted]

6.2. Secondary Endpoint(s)

6.2.1. Demographic and Physical Examination Data

Applicable to Parts A, and B – Analyses reported for each part separately.

A breakdown of demographic data will be provided for age, gender, race, and ethnicity. The physical measurement (weight, body mass index and height) at baseline will also be summarized. Each will be summarized by treatment and 'All Subjects' in accordance with the sponsor reporting standards.

For Part B only, an additional table summarizing the screening data of free T4, TSH, calcitonin, amylase, lipase, lipids, PT/INR/aPTT, TBA and HbA1c will be produced as above.

Finally, data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data (unless noted above) will be reported for randomized participants.

6.2.2. Discontinuation(s)

Applicable to Parts A and B – Analyses reported for each part separately.

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by treatment.

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

6.2.3. Adverse Events

Applicable to Parts A, and B – Analyses reported for each part separately:

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

Incidence and severity of treatment emergent adverse event (TEAE) tables will additionally be produced ('All causality' and 'Treatment related', separately) to summarise the total number of adverse events by preferred term, which will be reported by treatment group and overall in accordance with sponsor reporting standards using the safety analysis set defined in Section Section 4

6.2.4. Hypoglycemia (Part B only)

Any hypoglycemic AEs will be listed in a separate table and summarized categorically by treatment as per Section 5.2.3 using the safety population defined in Section 4

6.2.5. Laboratory Data

Applicable to Parts A, and B – Analyses reported for each part separately:

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards using the safety population defined in Section 4 Baseline is as defined in Section 3.4.

6.2.6. Vital Signs Data

Applicable to Parts A, and B – Analyses reported for each part separately:

Absolute values and change from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment, time post-dose and day, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.4.

Mean changes from baseline for supine systolic and diastolic blood pressure and pulse rate will be plotted against time post-dose and day. On each plot there will be 1 line for each treatment.

Maximum absolute values and changes from baseline for vital signs will be summarized descriptively by treatment using categories as defined in Section 5.2.3. Numbers and percentages of subjects meeting the categorical criteria will also be provided. All planned and unplanned post-dose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

6.2.7. Electrocardiogram (ECG)

Applicable to Parts A, and B – Analyses reported for each part separately.

Absolute values and changes from baseline in QT interval, heart rate, QTcF interval, PR interval and QRS interval will be summarized by treatment, time postdose, and day using sponsor reporting standards using the safety population defined in Section 4 Tables will be paged by parameter. Baseline is as defined in Section 3.4.

Mean changes from baseline in ECG parameters will be plotted against day. On each plot there will be 1 line for each treatment. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned post-dose time-points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Listings of subjects with any single post-dose value >500 msec will also be produced for QTcF.

QTcB will be listed only and not summarized.

6.2.8. C-SSRS (Part B Only)

Screening, baseline and post-baseline C-SSRS data (mapped to C-CASA scores as described in Section 3.2.2.1) using the safety population defined in Section 4 will be summarized categorically by treatment and time point as outlined in Section 5.2.3.

6.2.9. PHQ-9 (Part B only)

Baseline and post-baseline PHQ-9 data (responses to each of the 9 items) using the safety population defined in Section 4 will be summarized categorically for each question separtely by treatment and time point as outlined in Section 5.2.3.

6.3. Other Endpoint(s)

6.3.1. Change from Baseline in PT, INR, aPTT (Part B only)

- Estimand strategy: Not applicable
- Analysis set: Safety Population Set

Absolute values and change from baseline will be summarized descriptively by treatment and timepoint as described in Section 5.2.2

6.3.2. Change from Baseline in TSH, Lipids (Part B only)

- Estimand strategy: Not applicable
- Analysis set: Safety Population Set

Absolute values and change from baseline will be summarized descriptively by treatment and timepoint as described in Section 5.2.2

6.3.3. Change from Baseline in Free T4, Calcitonin, Amylase, Lipase, TBA (Part B only)

- Estimand strategy: Not applicable
- Analysis set: Safety Population Set

Absolute values and change from baseline will be summarized descriptively by treatment and timepoint as described in Section 5.2.2

6.3.4. Change from Baseline in Body Weight (Part B Only)

The change from baseline and percent change from baseline to all post-dose timepoints as specified in the SoA will be calculated.

- Estimand strategy: Not applicable
- Analysis set: Safety Population Set

Absolute values, change from baseline, and percent change from baseline will be summarized descriptively by treatment and day as per Section 5.2.2

6.3.5. Coproporphyrins I (Part B)

Estimand strategy: Not applicable

Analysis set: Endogenous biomarker Concentration and Parameter Population Set

To assess the effects of PF-06882961 on coproporphyrins I (CP-I) in Part B, the CP-I parameters detailed in Section 3.3 will be listed and summarized for participants in the endogenous biomarker analysis set (as defined in Section 4) . Missing values will be handled as detailed in Section 5.3 along with handling of values where participants received a dose that was not assigned based on the titration scheme). Each CP-I parameter will be summarized by treatment (eg differentiating different doses and dosing frequencies as required), Study Part and Study Day/Period (as appropriate).

The parameters will include the set of summary statistics as specified in the table below:

Table 7. CP-I Parameters to be Summarized Descriptively per Day

Part	Parameter	Days	Summary Statistics
[redacted]	AUC_{12}, $AUC_{12}/12$ (ie C_{av}), C_{max}	30 and 46	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

On Day 1, individual C_{av} and individual C_{max} will be the mean of CP-I plasma concentrations and will serve as baseline to calculate individual change from baseline for each parameter on Day 30 and Day 46. These individual calculated means will also be used for Day1 graphical presentations.

Change from baseline in C_{av} and C_{max} for CP-I will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect.

Estimates of the adjusted mean differences against the reference will be obtained and corresponding 90% CIs will be reported from the models. The test treatments will be "PF-06882961 120 mg BID" (Day 30) and "PF-06882961 200 mg BID" (Day 46) and reference treatment is "No PF-06882961" (Day 1).

There will be one summary table presenting all parameters. The treatment subheading will include the dose information and day (Day 1, Day 30 or Day 46). As per Section 5.3, data collected on days that participants received anything other than the assigned dose based on the titration scheme will only be listed and not summarized as part of the summary table.

The following plots will be presented:

- Box and whisker plots for individual parameters of CP-I (ie C_{av} and C_{max}) will be presented by treatment and overlaid with geometric means.

Presentations for CP-I concentrations will include:

- a listing of all concentrations sorted by participant ID, treatment, and nominal time postdose. 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 treatment, and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- median concentration time plots (on both linear and semi-log scales) against nominal time post-dose by treatment period. One plot for each scale will be presented which will include the different PF-06882961 treatment periods in the same plot.

- mean concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by treatment period. One plot for each scale will be presented which will include the different PF-06882961 treatment periods in the same plot.

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

For summary statistics, median and mean plots by sampling time, the nominal blood sampling time will be used; for individual participant plots by time, the actual blood sampling time will be used.

6.3.6. 4-β-hydroxycholesterol/Cholesterol Ratio

The percent change from baseline to all post-dose timepoints as specified in the SoA will be calculated.

- Estimand strategy: Not applicable

- Analysis set: Endogenous biomarker Concentration and Parameter Population Set

Absolute values, and percent change from baseline will be summarized descriptively by treatment and day as per Section 5.2.2

The following plot will be presented:

- Box and whisker plots will be presented by treatment and overlaid with geometric means.

6.4. Subset Analyses

Not applicable.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

For each part of the study, and for each endpoint defined in this statistical analysis, baseline assessment will be summarized by treatment as per Section 5.2.2 and Section 5.2.3.

6.5.2. Study Treatment Exposure

For each part of the study, participant treatment exposure groups will be reported. Frequency counts will be supplied for participant discontinuation(s) by treatment.

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

CCI [redacted]

6.5.4. Screening and Other Special Purpose Data

For each part of the study, prior medication(s) and non-drug treatment(s), serum FSH concentrations, urine drug screen, will be obtained at Screening.

These data will be listed.

7. INTERIM ANALYSES

Not applicable because, *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 assessment and facilitating dose-escalation decisions. In addition, these reviews may facilitate PK/PD modeling and/or supporting clinical development.*

8. REFERENCES

1. 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.

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Not Applicable fo this study

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

Not Applicable fo this study.

Appendix 2.2. Endpoint Derivations

Not Applicable fo this study

Appendix 2.3. Example SAS Code for Statistical Analyses

Appendix 2.3.1. Analysis for DDI interaction (Part A):

```
/* To compare Test PK Parameter to the Reference PK Parameter where l&var =
      log(&var)*
proc mixed data = input_dataset method = reml;
      class participant treatment period sequence;
      model l&var = treatment period sequence /ddfm = kr residual;
      random participant(sequence);
      lsmeans treatment;
      estimate 'trt1 – trt1' treatment  -1 1 / cl alpha = 0.1;
run;
```

Appendix 2.3.2. Analysis for DDI interaction (Part B):

```
/* To compare Test PK Parameter to the Reference PK Parameter where l&var = log(&var)*
proc mixed data=tab.pk;
      class Day Participant;
      model l&var= Day / ddfm=KR;
      random participant;
      lsmeans Day;
      Estimate 'Test vs Reference' Day -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;
```

Appendix 3. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AUC	area under the plasma concentration-time curve
AUC_{12}	area under the plasma concentration-time curve from time zero to time 12 hours post-dose
AUC_{24}	area under the plasma concentration-time curve from time zero to time 24 hours post-dose
AUC_{inf}	area under the plasma concentration-time curve from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (C_{last})
AV	atrioventricular
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CI	confidence interval
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent oral clearance
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease-19
CP-I	Coproporphyrins I
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
CV	coefficient of variation
DC	discontinuation
DDI	drug-drug interaction
DGAT	diacylglycerol acyltransferase
DILI	drug-induced liver injury

Abbreviation	Term
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EAC	event adjudication committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EFD	embryo-fetal development
ET	early termination
EudraCT	European Clinical Trials Database
F/U	follow-up
FAP	final approved protocol
FAS	full analysis set
FDA	Food and Drug Administration
f_m	fraction metabolized
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLIMMIX	generalized linear mixed-effects model with repeated measures
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide 1
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
HAE	hypoglycemic adverse event
HbA1c	hemoglobin A1c
HDL-C	high density lipoprotein cholesterol
HR	heart rate
ICD	informed consent document
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
ITT	intent-to-treat
IV	intravenous(ly)
k_{el}	elimination rate constant
K_i	apparent inactivation constant at half-maximal rate of inactivation
k_{inact}	maximal inactivation rate

Abbreviation	Term
LDL-C	low density lipoprotein cholesterol
LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	multi-drug resistance
MedDRA	Medical Dictionary for Regulatory Activities
MHP	mental health professional
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures
MMTT	mixed meal tolerance test
MNAR	missing not at random
CCI [redacted]	
mRNA	messenger ribonucleic acid
msec	millisecond
MTD	maximum tolerated dose
N/A	not applicable
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NNT	number needed to treat
NOAEL	no-observed-adverse-effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OATP1B1	organic anion transporting polypeptide 1B1
OCT	organic cation transporter
PD	pharmacodynamic(s)
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic(s)
PLT	platelet
PP	per-protocol
PPAS	per-protocol analysis set
PR	pulse rate
PT	prothrombin time

Abbreviation	Term
PVC	premature ventricular contraction/complex
QT	time from beginning of the QRS complex to the end of the T wave
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
R_{ac}	accumulation ratio
RBC	red blood cells
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGS	Statistical Guidance Standards
SoA	Schedule of Activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
T4	thyroxine
TA	therapeutic area
TBA	total bile acids
TEAE	treatment-emergent adverse event
TG	triglycerides
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
V_z/F	apparent oral volume of distribution
WBC	white blood cell
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary
WOCBP	woman of childbearing potential

Appendix 4. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

Absolute value of QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤60	>60	

Categories for PR and QRS

PR (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

Appendix 5. C-SSRS Mapped to C-CASA - Suicidal Ideation and Behavior Events and Codes

Table 1. C-SSRS Mapped to C-CASA (Suicidality Events and Codes)

Event Code	C-CASA Event	C-SSRS Response
Suicidal Ideation		
1	Passive	"Yes" on "Wish to be dead"
2	Active: Nonspecific (no method, intent, or plan)	"Yes" on "Non-Specific Active Suicidal Thoughts"
3	Active: Method, but no intent or plan	"Yes" on "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act"
4	Active: Method and intent, but no plan	"Yes" on "Active Suicidal Ideation with Some Intent to Act, without Specific Plan"
5	Active: Method, intent, and plan*	"Yes" on "Active Suicidal Ideation with Specific Plan and Intent"
Suicidal Behavior		
1	Completed suicide	"Yes" on "Completed Suicide"
2	Suicide attempt	"Yes" on "Actual Attempt"
3	Interrupted attempt	"Yes" on "Interrupted attempt"
4	Aborted attempt	"Yes" on "Aborted attempt"
5	Preparatory actions toward imminent suicidal behaviors	"Yes" on "Preparatory Acts or Behavior"
Self-injurious behavior, no suicidal intent		
	Self-injurious behavior, no suicidal intent	"Yes" on "Has subject engaged in Non-suicidal Self-Injurious Behavior?"

*According to C-SSRS, the definition of *plan* includes intent (i.e., intent to complete the suicide is implicit with the concept of plan). Thus, there is no need for the category *method and plan, but no intent*