Protocol C3421047

A PHASE 1, OPEN-LABEL, TWO-PART STUDY TO EVALUATE THE EFFECT OF TWO STEADY-STATE DOSE LEVELS OF PF-06882961 ON THE PHARMACOKINETICS OF SINGLE ORAL DOSES OF ATORVASTATIN AND MIDAZOLAM IN HEALTHY ADULTS AND AN ORAL CONTRACEPTIVE IN HEALTHY POST-MENOPAUSAL FEMALES

Statistical Analysis Plan
(SAP)

Version: 1.0

Date: 14 Oct 2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 14 Oct 2021	Original 30 Aug 2021	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 C3421047. 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.

This is a Phase 1, open-label, 2-part study to evaluate the effect of 2 steady-state dose levels of PF-06882961 on the single-dose *(SD) pharmacokinetics of 1) atorvastatin and midazolam in healthy adult male and female participants (Part A), and 2) an* oral contraceptive *(OC) in healthy* post-menopausal *(PM) female participants (Part B). The intent of this study is to generate safety, tolerability, and pharmacokinetic data for further clinical development.*

2.1. Study Objectives, Endpoints, and Estimands

Objectives	***Endpoints***
Part A	
Primary:	***Primary***
• *To evaluate the effects of PF-06882961 on the pharmacokinetics of atorvastatin in healthy male and female adult participants.* • *To evaluate the effects of PF-06882961 on the pharmacokinetics of midazolam in healthy male and female adult participants.*	• *Atorvastatin plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 4 and 7.* • *Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 2, 5 and 8.*
Secondary:	***Secondary:***
• *To evaluate the safety and tolerability of PF-06882961 administered separately and in combination with atorvastatin or midazolam in healthy male and female adult participants.*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters during Part A of the study.* • *Assessment of mental health as determined by C-SSRS and PHQ-9 during Part A of the study.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
• *To evaluate the effects of PF-06882961 on additional pharmacokinetic parameters of atorvastatin and midazolam in healthy male and female adult participants.*	• *Additional plasma pharmacokinetic parameters for atorvastatin (Periods 1, 4 and 7) and midazolam (Periods 2, 5 and 8):*

	C_{max} and T_{max}; and CL/F, Vz/F, $t_{½}$, as data permit.
• *To evaluate the MD pharmacokinetics of PF-06882961 in healthy male and female adult participants.* • *To evaluate the effects of PF-06882961 on the pharmacokinetics of ortho-hydroxyatorvastatin in healthy male and female adult participants.* • *To evaluate the effects of PF-06882961 on the pharmacokinetics of 1-OH-midazolam in healthy male and female adult participants* • *To evaluate the effects of PF-06882961 on biomarkers of CYP3A induction. [Optional].*	• *PF-06882961 plasma pharmacokinetic parameters at Days 35 and 58: AUC_{24}, C_{max}, T_{max}.* • *Ortho-hydroxyatorvastatin plasma pharmacokinetic parameters: AUC_{last}, C_{max}, T_{max}; and AUC_{inf} and $t_{½}$ as data permit in Periods 1, 4 and 7. Metabolite/parent (ortho-hydroxyatorvastatin/atorvastatin) ratios will also be calculated.* • *1-OH-midazolam plasma pharmacokinetic parameters: AUC_{last}, C_{max}, T_{max}; and AUC_{inf} and $t_{½}$ as data permit in Periods 2, 5 and 8. Metabolite/parent (1-OH-midazolam/midazolam) ratios will also be calculated.* • *Morning predose 4-β-hydroxycholesterol/cholesterol plasma ratio on Day 1 in Periods 2, 5, and 8. Morning predose plasma-derived EV on Day 1 in Periods 2, 5, and 8.*
Part B	
Primary:	***Primary:***
• *To evaluate the effects of PF-06882961 on the pharmacokinetics of an OC (LE/EE) in healthy PM female participants.*	• *LE plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 3 and 5.* • *EE plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 3 and 5.*

Secondary:	***Secondary:***
• To evaluate the safety and tolerability of PF-06882961 administered separately and in combination with an OC (LE/EE) in healthy PM female participants.	*• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters during Part B of the study.* *• Assessment of mental health as determined by C-SSRS and PHQ-9 during Part B of the study.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
• To evaluate the effects of PF-06882961 on additional pharmacokinetic parameters of an OC (LE/EE), administered separately, in healthy PM female participants. *• To evaluate the pharmacokinetics of multiple doses of PF-06882961 in healthy PM female participants*	*• Additional plasma pharmacokinetic parameters for LE and EE (both in Periods 1, 3 and 5): C_{max}, T_{max}; and CL/F, Vz/F, $t_{½}$ as data permit.* *• PF-06882961 plasma pharmacokinetic parameters at Days 36 and 60: AUC_{24}, C_{max}, T_{max}.*
**Should it be deemed that too few AUC_{inf} estimates (eg, less than 12 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary endpoint for CSR reporting. This will be considered for the atorvastatin, midazolam, LE, and EE objectives separately.*	

There are no estimands for this study.

2.2. Study Design

This study will be conducted in 2 parts. Part A will evaluate the effect of 2 steady-state dose levels of PF-06882961 on the SD pharmacokinetics of atorvastatin and midazolam. Part B will evaluate the effect of 2 steady-state dose levels of PF-06882961 on the SD pharmacokinetics of an OC. Participants will participate in either Part A or Part B (not both), and Parts A and B are *expected to be conducted in parallel, if possible. Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and Sponsor.*

2.2.1. Part A

Part A of this study is an open-label, 8-period, fixed-sequence study to evaluate the effect of PF-06882961, administered at 2 PK steady-state dose levels, on the SD PK of atorvastatin and midazolam, administered separately, in healthy adult male and female participants with a BMI ranging from 20.0 kg/m^2 to <30.0 kg/m^2. Approximately 16 subjects will be enrolled in Part A. The total duration of participation from the Screening Visit (28 days) to the FU

contact will be approximately 18 weeks; ie, 125 days, of which 64 days will be in-house as shown in Figure 1.

Figure 1 Part A Study Design

The FU visit will occur 7-10 days from the last dose of study intervention and a FU contact will occur 28-35 days from the last dose of study intervention.

2.2.2. Part B

Part B of this study is an open-label, 5-period, fixed-sequence study to evaluate the effect of PF-06882961, administered at 2 PK steady-state dose levels, on the SD PK of an OC (LE and EE) in healthy, PM female participants with a BMI ranging from 20.0 kg/m^2 to <30.0 kg/m^2. Approximately 16 subjects will be enrolled in Part B. The total duration of participation from the Screening Visit (28 days) to the FU contact will be approximately 18 weeks; ie, 125 days, of which 67 days will be in-house as shown in Figure 2.

Figure 2 Part B Study Design

The FU visit will occur 7-10 days from the last dose of study intervention and a FU contact will occur 28-35 days from the last dose of study intervention.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Blood samples for pharmacokinetic (PK) analysis of atorvastatin, ortho-hydroxyatorvastatin, midazolam, 1-OH-midazolam, levonorgestrel (LE), ethinyl estradiol (EE) and PF-06882961 will be collected according to the Schedule of Activities given in the protocol.

PK parameters will be calculated (if possible) from the concentration-time data using standard noncompartmental methods.

3.1. Primary Endpoint(s)

3.1.1. Part A

- *Atorvastatin plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 4 and 7.*
- *Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 2, 5 and 8.*

**Should it be deemed that too few AUC_{inf} estimates (eg, less than 12 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary*

endpoint for CSR reporting. This will be considered for the atorvastatin and midazolam objectives separately.

AUC_{last} will be calculated and reported regardless of whether AUC_{inf} is the primary endpoint for CSR reporting or not. The plasma PK parameters in Table 2 will be determined using standard non-compartmental methods:

Table 2. Summary of primary atorvastatin and midazolam plasma PK parameters to be calculated

Parameter	Analysis Scale	Atorvastatin 20 mg (Periods 1, 4 and 7)	Midazolam 5 mg (Periods 2, 5 and 8)
AUC_{inf}*	ln	A, D	A, D
AUC_{last}	ln	A, D	A, D

*=if data permit. Abbreviations: A=analyzed using a statistical model; D=displayed with descriptive statistics; ln=natural-log transformed.

3.1.2. Part B

- *LE plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 3 and 5.*
- *EE plasma pharmacokinetic parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 3 and 5.*

**Should it be deemed that too few AUC_{inf} estimates (eg, less than 12 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary endpoint for CSR reporting. This will be considered for the LE and EE objectives separately.*

AUC_{last} will be calculated and reported regardless of whether AUC_{inf} is the primary endpoint for CSR reporting or not. The plasma PK parameters in Table 3 will be determined using standard non-compartmental methods:

Table 3. Summary of primary LE and EE plasma PK parameters to be calculated

Parameter	Analysis Scale	LE 0.15 mg (Periods 1, 3 and 5)	EE 0.03 mg (Periods 1, 3 and 5)
AUC_{inf}*	ln	A, D	A, D
AUC_{last}	ln	A, D	A, D

*=if data permit. Abbreviations: A=analyzed using a statistical model; D=displayed with descriptive statistics; ln=natural-log transformed.

3.2. Secondary Endpoint(s)

3.2.1. Safety Endpoints

- *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters during Part A of the study.*

- *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters during Part B of the study.*

All safety endpoints will be considered separately for the two parts of the 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,
- Electrocardiogram (ECG) results.

For laboratory, vital signs and ECG data there will be two separate definitions for baseline that will be calculated separately (where applicable):

i) using a fixed baseline of the last pre-dose measurement in Period 1. (“Baseline 1”)
ii) using a fixed baseline of the last pre-dose measurement in Period 2 (Part B) or Period 3 (Part A). (“Baseline 2”)

Change from baseline will therefore be calculated twice for each relevant safety endpoint using (i) and (ii) above. Data collected in Periods 1 and 2 (Part A only) will not have a change from baseline calculated based on the 2nd definition.

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

3.2.2. Assessment of Mental Health

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

- *Assessment of mental health as determined by C-SSRS and PHQ-9 during Part B of the 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 3

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 schedule of activities (SoA).

*The SoA can be found in Section 1 of the protocol.

The PHQ-9 total score will be derived for each time point separately by summing the responses to the 9 questions.

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

3.2.3. Exploratory Safety Endpoints

- Change from baseline in body weight at all post-dose time points as outlined in the SoA
- Percent change from baseline in body weight at all post-dose time points as outlined in the SoA
- Change from baseline in fasting plasma glucose at all post-dose time points as outlined in the SoA
- Change from baseline in HbA1c at all post-dose time points as outlined in the SoA

There will be two separate definitions for baseline that will be calculated separately:

i) using a fixed baseline of the last pre-dose measurement in Period 1. ("Baseline 1")

ii) using a fixed baseline of the last pre-dose measurement in Period 2 (Part B) or Period 3 (Part A). ("Baseline 2")

Change from baseline will therefore be calculated twice for the above endpoints. Data collected in Periods 1 and 2 (Part A only) will not have a change from baseline calculated based on the 2nd definition.

3.3. Other Endpoint(s)

3.3.1. Part A

3.3.1.1. Additional plasma PK Parameters for atorvastatin and midazolam

- *Additional plasma pharmacokinetic parameters for atorvastatin (Periods 1, 4 and 7) and midazolam (Periods 2, 5 and 8): C_{max} and T_{max}; and CL/F, Vz/F, $t_{½}$, as data permit.*

The additional plasma PK parameters for atorvastatin and midazolam in Table 4 will be determined using standard non-compartmental methods:

Table 4. Summary of additional atorvastatin and midazolam plasma PK parameters to be calculated

Parameter	Analysis Scale	Atorvastatin 20mg (Periods 1, 4 and 7)	Midazolam 5mg (Periods 2, 5 and 8)
C_{max}	ln	A, D	A, D
T_{max}	R	D	D
$t_{1/2}$*	R	D	D
CL/F*	ln	D	D
Vz/F*	ln	D	D

*=if data permit. Abbreviations: A=analyzed using a statistical model; D=displayed with descriptive statistics; ln=natural-log transformed; R=raw (untransformed).

3.3.1.2. Plasma PK Parameters for PF-06882961

- *PF-06882961 plasma pharmacokinetic parameters at Days 35 and 58: AUC_{24}, C_{max}, T_{max}.*

The plasma PK parameters for PF-06882961 in Table 5 will be determined using standard non-compartmental methods.

Table 5. Summary of PF-06882961 plasma PK parameters to be calculated

Parameter	Analysis Scale	PF-06882961 120mg (Day 35)	PF-06882961 200mg (Day 58)
AUC_{24}	ln	D	D
C_{max}	ln	D	D
T_{max}	R	D	D

Abbreviations: D=displayed with descriptive statistics; ln=natural-log transformed; R=raw (untransformed).

3.3.1.3. Plasma PK Parameters for Ortho-hydroxyatorvastatin and 1-OH-midazolam

- *Ortho-hydroxyatorvastatin plasma pharmacokinetic parameters: AUC_{last}, C_{max}, T_{max}; and AUC_{inf} and $t_{½}$ as data permit in Periods 1, 4 and 7. Metabolite/parent (ortho-hydroxyatorvastatin/atorvastatin) ratios will also be calculated.*

- *1-OH-midazolam plasma pharmacokinetic parameters: AUC_{last}, C_{max}, T_{max}; and AUC_{inf} and $t_{½}$ as data permit in Periods 2, 5 and 8. Metabolite/parent (1-OH-midazolam/midazolam) ratios will also be calculated.*

The plasma PK parameters for ortho-hydroxyatorvastatin and 1-OH-midazolam in Table 6 will be determined using standard non-compartmental methods.

Table 6. Summary of ortho-hydroxyatorvastatin and 1-OH-midazolam plasma PK parameters to be calculated

Parameter	Analysis Scale	Atorvastatin 20mg (Periods 1, 4 and 7)	Midazolam 5mg (Periods 2, 5 and 8)
AUC_{inf}*	ln	D	D
AUC_{last}	ln	D	D
C_{max}	ln	D	D
T_{max}	R	D	D
$t_{1/2}$*	R	D	D
Metabolite/parent AUC_{inf}* ratio[a] ($MRAUC_{inf}$)	R	D	D
Metabolite/parent AUC_{last} ratio[a] ($MRAUC_{last}$)	R	D	D

Metabolite/parent C_{max} ratio[a] (MRC_{max})	R	D	D

*If data permit. [a]Determined as both ortho-hydroxyatorvastatin AUC or C_{max} / atorvastatin AUC or C_{max} and 1-OH-midazolam AUC or C_{max} / midazolam AUC or C_{max} separately as applicable. Abbreviations: D=displayed with descriptive statistics; ln=natural-log transformed; R=raw (untransformed).

3.3.1.4. Biomarkers of CYP3A Induction (Optional)

- *Morning predose 4-β-hydroxycholesterol/cholesterol plasma ratio on Day 1 in Periods 2, 5, and 8. Morning predose plasma-derived EV on Day 1 in Periods 2, 5, and 8.*

The associated objective related to these endpoints is optional and the results may not be reported in the CSR.

Table 7. Summary of parameters to be calculated for exploratory analysis

Parameter	Analysis Scale	Morning predose Measurement (Periods 2, 5, 8 Day 1)
4-β-hydroxycholesterol concentration	R	D
Cholesterol concentration	R	D
4-β-hydroxycholesterol/cholesterol plasma ratio	R	D
EV concentration	R	D

Abbreviations: D=displayed with descriptive statistics; R=raw (untransformed).

For the parameters listed in Table 7, baseline will be defined as the measurement taken predose at Day 1 on Period 2. The percent change from baseline in plasma ratios of 4-β-hydroxycholesterol/cholesterol will additionally be calculated by first calculating the ratios, then the percent change from baseline at each post-dose time point (Day 1 in Periods 5 and 8).

3.3.2. Part B

3.3.2.1. Additional plasma PK Parameters for LE and EE

- *Additional plasma pharmacokinetic parameters for LE and EE (both in Periods 1, 3 and 5): C_{max}, T_{max}, CL/F, Vz/F, $t_{½}$, as data permit.*

The additional plasma PK parameters for LE and EE in Table 8 will be determined using standard non-compartmental methods

Table 8. Summary of additional LE and EE plasma PK Parameters to be calculated

Parameter	Analysis Scale	LE 0.15 mg (Periods 1, 3 and 5)	EE 0.03 mg (Periods 1, 3 and 5)
C_{max}	ln	A, D	A, D
T_{max}	R	D	D
$t_{1/2}$*	R	D	D
CL/F*	ln	D	D
Vz/F*	ln	D	D

*=if data permit. Abbreviations: A=analyzed using a statistical model; D=displayed with descriptive statistics; ln=natural-log transformed; R=raw (untransformed).

3.3.2.2. Plasma PK Parameters for PF-06882961

- *PF-06882961 plasma pharmacokinetic parameters at Days 36 and 60: AUC_{24}, C_{max}, T_{max}*

The PK parameters for PF-06882961 in Table 9 will be determined using standard non-compartmental methods.

Table 9. Summary of PF-06882961 plasma PK parameters to be calculated

Parameter	Analysis Scale	PF-06882961 120 mg (Day 36)	PF-06882961 200 mg (Day 60)
AUC_{24}	ln	D	D
C_{max}	ln	D	D
T_{max}	R	D	D

Abbreviations: D=displayed with descriptive statistics; ln=natural log-transformed; R=raw (untransformed).

3.3.3. Banked Biospecimens

Banked biospecimens will be collected and retained for future analyses, but will not be analyzed specifically for this study and will not be included in the CSR.

3.4. Baseline Variables

Not Applicable.

3.5. Safety Endpoints

See Section 3.2 for details.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

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. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
Evaluable	*All participants assigned to study intervention and who take at least 1 dose of study intervention.*
Safety	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.*
PK Concentration Set	*The PK concentration population is defined as all participants who received at least 1 dose of atorvastatin, midazolam, an oral contraceptive and/or PF-06882961 and in whom at least 1 plasma concentration value is reported.*
PK Parameter Set	*The PK parameter analysis population is defined as all participants who received at least 1 dose of atorvastatin, midazolam, an oral contraceptive and/or PF-06882961 and have at least 1 of the PK parameters of interest calculated. Should vomiting occur after co-administration of atorvastatin, midazolam, or the oral contraceptive with PF-06882961, the resulting PK parameters from that participant from the corresponding period may be excluded, where further details are provided* in Section 5.3

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing planned for this study and no statistical decision rules will be applied.

5.2. General Methods

5.2.1. Treatment Labels and Groupings

5.2.1.1. Part A

Unless otherwise stated, all summaries and plots will be presented by treatment group (equivalent to 'by Period'). The following treatment labels (or similar) will be used, which represent Periods 1 to 8 as:

Period	Treatment Label
1	Atorvastatin 20mg (Period 1)
2	Midazolam 5mg (Period 2)
3	PF-06882961 titration up to 120mg BID (Period 3)
4	PF-06882961 120mg BID + Atorvastatin 20mg (Period 4)
5	PF-06882961 120mg BID + Midazolam 5mg (Period 5)
6	PF-06882961 titration up to 200mg BID (Period 6)
7	PF-06882961 200mg BID + Atorvastatin 20mg (Period 7)
8	PF-06882961 200mg BID + Midazolam 5mg (Period 8)

5.2.1.2. Part B

Unless otherwise stated, all summaries and plots will be presented by treatment group (equivalent to 'by Period'). The following treatment labels (or similar) will be used, which represent Periods 1 to 5 as:

Period	Treatment Label
1	0.15mg LE & 0.03mg EE (Period 1)
2	PF-06882961 titration up to 120mg BID (Period 2)
3	PF-06882961 120mg BID + 0.15mg LE & 0.03mg EE (Period 3)
4	PF-06882961 titration up to 200mg BID (Period 4)
5	PF-06882961 200mg BID + 0.15mg LE & 0.03mg EE (Period 5)

5.2.2. Analyses for Continuous Endpoints

Unless otherwise stated, continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values.

5.2.3. Analyses for Categorical Endpoints

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

5.2.4. Mixed Effects Model

A mixed effects model with treatment as a fixed effect and participant as a random effect will be used. *Estimates of the adjusted mean differences (Test-reference) and corresponding 90%* confidence intervals (*CIs*) *will be obtained from the models. 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.*

This model will be applied separately to Part A and Part B.

The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and the Kenward-Roger degrees of freedom algorithm. Example code is shown in Appendix 1.

5.3. Methods to Manage Missing Data

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

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).

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

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

1. A concentration has been collected as ND (i.e. not done) or NS (i.e. no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist/statistician.

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

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

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

5.3.1. Plasma PK Parameters

Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (i.e. not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular treatment group/analyte with ≥3 evaluable measurements. For statistical analyses (i.e. mixed effects model), PK parameters coded as NC will also be set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual participant has a known biased estimate of a plasma PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body, e.g. within 2 times the median T_{max} after the last dose for the respective treatment [1]), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

6. ANALYSES AND SUMMARIES

For all presentations, study day will refer to the day within a particular treatment period, unless otherwise specified.

6.1. Primary Endpoint(s)

6.1.1. Part A

6.1.1.1. AUC_{inf} and AUC_{last} for atorvastatin and midazolam

AUC_{inf} and AUC_{last} for atorvastatin and midazolam alone and co-administered with PF-06882961 will be listed, summarized descriptively and analyzed by treatment for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

Natural $\log_e$ transformed AUC_{inf} (as data permit) of atorvastatin administered alone or co-administered with PF-06882961 will be analyzed using a mixed effect model as described in Section 5.2.4. *The 2 test treatments will be 'atorvastatin and PF-06882961 120 mg BID' (Period 4) and 'atorvastatin and PF-06882961 200 mg BID' (Period 7), which will be reported separately in comparison to the reference treatment of 'atorvastatin alone' (Period 1).* The same analysis will also be performed for natural $\log_e$-transformed AUC_{last} of atorvastatin.

Natural $\log_e$ transformed AUC_{inf} (as data permit) and AUC_{last} of midazolam administered alone or co-administered with PF-06882961 will be analyzed and reported separately using the same mixed effect model as described above for atorvastatin. *The 2 test treatments will be 'midazolam and PF-06882961 120 mg BID' (Period 5) and 'midazolam and PF-06882961 200 mg BID' (Period 8), which will be reported separately in comparison to the reference treatment of 'midazolam alone' (Period 2).*

In the event that participants do not successfully titrate to the target PF-06882961 doses by the end of Periods 3 and/or 6, the related PK parameters for atorvastatin and midazolam in the subsequent periods would not be included in the above models (but may be included in sensitivity analyses described below). Note this implies that evaluable PK parameters for the same participants from at least Period 1 (for atorvastatin) and 2 (for midazolam) would be included in the models.

AUC_{inf} and AUC_{last} will be summarized for each treatment (atorvastatin and midazolam will be reported in separate tables) as specified in Table 10.

Table 10. Summary statistics for primary PK parameters for atorvastatin and midazolam

Parameter	Summary Statistics
AUC_{inf} & AUC_{last}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

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

The following plots will be presented:

- Box and whisker plots for individual PK parameters (AUC_{inf} and AUC_{last}) will be presented by treatment and overlaid with geometric means and individual datapoints. These will be produced for atorvastatin and midazolam PK parameters separately.

6.1.1.1.1. Sensitivity/Supplementary Analyses

In the event that fewer than 12 participants have PK parameters of atorvastatin and/or midazolam related to co-administration with PF-06882961 200mg BID, the following sensitivity analyses will be considered for reporting:

- If at least 4 participants reached the same maximum tolerated dose (MTD) of PF-06882961 (≥160mg BID, but not 200mg BID) with associated PK parameters estimated, this data may be included in the model and the PF-06882961 dose would be reported as an additional 'test' treatment (compared to the reference treatment of atorvastatin/midazolam alone) in the mixed effects models described above. This data may also be reported as a separate treatment group for all associated PK parameter summaries (e.g. in separate summaries of atorvastatin, midazolam and PF-06882961 PK parameters)
- If fewer than 4 participants have PK parameters related to co-administration with PF-06882961 200mg BID, this data may be excluded from the mixed effects models and the dose wouldn't be reported as part of the model output. These data may also not be reported in associated PK parameter summaries (including PF-06882961 PK parameters)
- If there are multiple different MTDs of PF-06882961, all related PK parameters would be included in the model and the dose of PF-06882961 would be included as a continuous covariate (rather than factor). These doses may be reported as separate treatment groups for all associated PK parameter summaries depending on the minimum number of participants per group

If conducted, the above sensitivity analyses may replace the primary mixed effects models described above. Furthermore, an additional physiologically-based PK or other related model may be explored if fewer than 12 participants have PK parameters as above to further characterize the relationship between PK of PF-06882961 and PK of atorvastatin and/or midazolam, which would be reported outside of the CSR.

6.1.2. Part B

6.1.2.1. AUC_{inf} and AUC_{last} for LE and EE

AUC_{inf} and AUC_{last} for LE and EE alone and co-administered with PF-06882961 will be listed, summarized descriptively and analyzed by treatment for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

Natural log_e-transformed AUC_{inf} (as data permit) and AUC_{last} of LE and EE administered alone or co-administered with PF-06882961 will be analyzed and reported separately using the same mixed effect model as described for atorvastatin in Section 6.1.1.1. *For LE, the 2 test treatments will be 'LE and PF-06882961 120mg BID' (Period 3) and 'LE and PF-06882961 200mg BID' (Period 5), which will be reported separately in comparison to the reference treatment of 'LE alone' (Period 1). Similarly for EE, the 2 test treatments will be ' EE and PF-06882961 120mg BID' (Period 3) and ' EE and PF-06882961 200mg BID' (Period 5), which will be reported separately in comparison to the reference treatment of ' EE alone' (Period 1).*

In the event that participants do not successfully titrate to the target PF-06882961 doses by the end of Periods 2 and/or 4, the related PK parameters for LE and EE in the subsequent periods would not be included in the above models (but may be included in sensitivity analyses described below). Note this implies that evaluable PK parameters for the same participants from at least Period 1 would be included in the models.

AUC_{inf} and AUC_{last} will be summarized for LE and EE (reported in separate tables) as specified in Table 11.

Table 11. Summary statistics for primary PK parameters for LE and EE

Paramater	Summary Statistics
AUC_{inf} & AUC_{last}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

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

The following plots will be presented:

- Box and whisker plots for individual PK parameters (AUC_{inf} and AUC_{last}) will be presented by treatment and overlaid with geometric means and individual datapoints. These will be produced for LE and EE PK parameters separately.

6.1.2.1.1. Sensitivity/Supplementary Analyses

In the event that fewer than 12 participants have PK parameters LE and EE related to co-administration with PF-06882961 200 mg BID, the following sensitivity analyses will be considered for reporting:

- If at least 4 participants reached the same maximum tolerated dose (MTD) of PF-06882961 (≥160 mg BID, but not 200 mg BID) with associated PK parameters estimated, this data may be included in the model and the PF-06882961 dose would be reported as an additional 'test' treatment (compared to the reference treatment of LE/EE alone) in the mixed effects models described above. This data may also be reported as a separate treatment group for all associated PK parameter summaries (e.g. in separate summaries of LE, EE and PF-06882961 PK parameters)
- If fewer than 4 participants have PK parameters related to co-administration with PF-06882961 200 mg BID, this data may be excluded from the mixed effects models and the dose wouldn't be reported as part of the model output. These data may also not be reported in associated PK parameter summaries and listings (including PF-06882961 PK parameters)
- If there are multiple different MTDs of PF-06882961, all related PK parameters would be included in the model and the dose of PF-06882961 would be included as a continuous covariate (rather than factor). These doses may be reported as separate treatment groups for all associated PK parameter summaries depending on the minimum number of participants per group

If conducted, the above sensitivity analyses may replace the primary mixed effects models described above. Furthermore, an additional physiologically-based PK or other related model may be explored if fewer than 12 participants have PK parameters as above to further characterize the relationship between PK of PF-06882961 and PK of LE and/or EE, which would be reported outside of the CSR.

6.2. Secondary Endpoint(s)

Secondary endpoints will be reported separately for Part A and Part B of the study.

6.2.1. Adverse Events

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

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

The AEs will be presented sorted in descending frequency based on the overall number of AEs (by preferred term or system order class as appropriate) across treatments.

6.2.2. Laboratory Data

Laboratory data will be listed and summarized by treatment and overall, in accordance with the sponsor reporting standards using the safety population defined in Section 4. Change from baseline summaries will be presented separately for each of the baselines defined in Section 3.2.1. Laboratory abnormality summary and listing tables will only be produced for Baseline 1. In summary and listing tables, laboratory abnormalities occurring pre-dose on Day 1 during Periods 2-8 (Part A) or Periods 2-5 (Part B) will be attributed to the treatment from the previous Period (e.g. an occurrence pre-dose at Period 3 Day 1, will be attributed to the Period 2 treatment).

6.2.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment and time point, according to sponsor reporting standards using the safety population defined in Section 4. Summaries will be presented separately for each of the baselines defined in Section 3.2.1.

Mean absolute values and mean changes from baseline for systolic and diastolic blood pressure and pulse rate will be plotted against time point. On each plot there will be 1 line for each treatment with all treatments on the same plot. Corresponding individual plots of changes from baseline will also be produced for each treatment. These will be produced separately for each of the baselines defined in Section 3.2.1.

Maximum and minimum absolute values and changes from baseline for supine vital signs will also be summarized descriptively by treatment using categories as defined in Appendix 2. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post dose time points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed. These will be produced for Baseline 1 only as defined in Section 3.2.1. Values meeting the categorical criteria occurring pre-dose on Day 1 during Periods 2-8 (Part A) or Periods 2-5 (Part B) will be attributed to the treatment from the previous Period (e.g. an occurrence pre-dose at Period 3 Day 1, will be attributed to the Period 2 treatment).

6.2.4. Electrocardiogram (ECG)

Absolute values and changes from baseline in QT interval, heart rate, Fridericia method corrected QT (QTcF) interval, pule rate (PR) interval and QRS interval will be summarized by treatment and time point using sponsor reporting standards using the safety population defined in Section 4. Tables will be paged by parameter. Summaries will be presented separately for each of the baselines defined in Section 3.2.1.

Mean changes from baseline for QT interval, heart rate and QTcF interval will be plotted against time point. On each plot there will be 1 line for each treatment with all treatments included on the same plot. Corresponding individual plots of changes from baseline will also be produced for each treatment. These will be produced separately for each of the baselines defined in Section 3.2.1.

Maximum absolute values and changes from baseline for QTcF, PR and QRS will also be summarized descriptively by treatment using categories as defined in Appendix 2. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post dose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed. These will be produced for Baseline 1 only as defined in Section 3.2.1. Values meeting the categorical criteria occurring pre-dose on Day 1 during Periods 2-8 (Part A) or Periods 2-5 (Part B) will be attributed to the treatment from the previous Period (e.g. an occurrence pre-dose at Period 3 Day 1, will be attributed to the Period 2 treatment).

6.2.5. C-SSRS

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.

6.2.6. PHQ-9

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 separately by treatment and time point as outlined in Section 5.2.3. The PHQ-9 total score as defined in Section 3.2.2.2 will additionally be summarized descriptively by treatment group and time point as outlined in Section 5.2.2.

6.2.7. Mental Health Risk Assessment

The number of participants who met the criteria for referral to a mental health professional will be listed and summarized by treatment group and time point as outlined in Section 5.2.3.

6.2.8. Exploratory Safety Endpoints

Absolute values and changes from baseline for body weight (both absolute and percent change, separately), fasting glucose and HbA1c will summarized by treatment and time point as outlined in Section 5.2.2 using the safety population defined in Section 4. These will be produced separately for each of the baselines defined in Section 3.2.3.

6.3. Other Endpoint(s)

6.3.1. Part A

6.3.1.1. Additional plasma PK Parameters for atorvastatin and midazolam

C_{max}, T_{max}, CL/F, Vz/F, $t_{½}$ for atorvastatin and midazolam alone and co-administered with PF-06882961 will be listed, summarized descriptively and analyzed by treatment for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

C_{max}, T_{max}, CL/F, Vz/F, $t_{½}$ will be summarized for each treatment (atorvastatin and midazolam will be reported in separate tables) as specified in Table 12.

Table 12. Summary statistics for additional plasma PK parameters for atorvastatin and midazolam

Parameter	Summary Statistic
C_{max}, CL/F, Vz/F	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$*	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

*if data permits.

Natural log-transformed C_{max} of atorvastatin administered alone or co-administered with PF-06882961 will be analyzed using a mixed effects model as described in Section 5.2.4, using the same approach as outlined in Section 6.1.1.1 for AUC_{inf} and AUC_{last}. The same mixed effects analysis will also be performed for natural log-transformed C_{max} of midazolam.

The following plots will be presented:

- Box and whisker plots for individual C_{max} values will be presented by treatment and overlaid with geometric means and individual datapoints. These will be produced for atorvastatin and midazolam PK parameters separately.

The following summaries will additionally be presented for the plasma concentration data of atorvastatin and midazolam (reported in separate tables) using the PK Concentration Set (as defined in Section 4):

- A listing of all concentrations sorted by participant ID and nominal time post-dose for each treatment and analyte (i.e. atorvastatin or midazolam) separately. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by each nominal time post-dose (produced separately for each treatment and 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.
- Median concentration time plots (on both linear and semi-log scales) against nominal time post-dose by treatment. Two plots will be presented for each scale: one for the three treatments with atorvastatin and another for the three treatments with midazolam.
- Individual concentration time plots by treatment (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each treatment, with a line for each participant per scale). Plots for atorvastatin and midazolam will be produced separately.
- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time post-dose. Two plots for each participant and scale will be presented: one for the three treatments with atorvastatin and one for the three treatments with midazolam.

The nominal PK sampling time will be used for summary statistics and relevant median plots, whereas for individual participant plots by time, the actual PK sampling time will be used.

6.3.1.2. Plasma PK Parameters for PF-06882961

Plasma PK parameters for PF-06882961 as described in Section 3.3.1.2 will be listed and summarized descriptively for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

AUC_{24}, C_{max}, T_{max}, will be summarized for each treatment period of PF-06882961 as required in Table 13.

Table 13. Summary statistics for plasma PK parameters for PF-06882961

Parameter	Summary Statistics
AUC_{24}, C_{max}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%

T_{max}	N, median, minimum, maximum.

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 and individual datapoints.

The following summaries will additionally be presented for the plasma concentration data of PF-06882961 using the PK Concentration Set (as defined in Section 4):

- A listing of all concentrations sorted by participant ID and nominal time post-dose for each PF-06882961 treatment period separately. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by each nominal time post-dose (produced separately for each treatment period), 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 both 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).
- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time post-dose. One plot for each participant and scale will be presented which will include both PF-06882961 treatment periods in the same plot.

The nominal PK sampling time will be used for summary statistics and relevant median plots, whereas for individual participant plots by time, the actual PK sampling time will be used.

6.3.1.3. Ortho-hydroxyatorvastatin and 1-OH-midazolam

AUC_{inf}*, AUC_{last}, C_{max}, T_{max}, $t_{½}$* and the respective metabolite/parent AUC_{inf}*, AUC_{last} and C_{max} ratios for ortho-hydroxyatorvastatin and 1-OH-midazolam alone and co-administered with PF-06882961 will be listed and summarized descriptively by treatment for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

AUC_{inf}*, AUC_{last}, C_{max}, T_{max}, $t_{½}$* and the respective metabolite/parent AUC_{inf}*, AUC_{last} and C_{max} ratios will be summarized for each metabolite (ortho-hydroxyatorvastatin and 1-OH-midazolam will be reported in separate tables) as specified Table 14.

Table 14. Summary statistics for plasma PK parameters for ortho-hydroxyatorvastatin and 1-OH-midazolam

Parameter	Summary Statistics
AUC_{inf}*, AUC_{last}, C_{max}, metabolite/parent ratios	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$*	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

*if data permit.

Natural log-transformed AUC_{inf}*, AUC_{last} and C_{max} for ortho-hydroxyatorvastatin and 1-OH-midazolam alone and co-administered with PF06882961 will be analyzed separately using a mixed effects model as described in Section 5.2.4, using the same approach as outlined in Section 6.1.1.1 for AUC_{inf} and AUC_{last}. This will produce 6 separate modelled results for the different metabolite parameters.

The following plots will be presented:

- Box and whisker plots for individual PK parameters (AUC_{inf}*, AUC_{last}, C_{max} and metabolite/parent ratios) will be presented by treatment and overlaid with geometric means and individual datapoints. These will be produced for ortho-hyrodyatorvastatin and 1-OH-midazolam PK parameters separately.

The following summaries will additionally be presented for the plasma concentration data of ortho-hydroxyatorvastatin and 1-OH-midazolam (reported in separate tables) using the PK Concentration Set (as defined in Section 4):

- A listing of all concentrations sorted by participant ID and nominal time post-dose for each treatment and analyte (i.e. ortho-hydroxyatorvastatin or 1-OH-midazolam) separately. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by each nominal time post-dose (produced separately for each treatment and 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.
- Median concentration time plots (on both linear and semi-log scales) against nominal time post-dose by treatment. Two plots will be presented for each scale: one for ortho-hydroxyatorvastatin and another for 1-OH-midazolam.

- Individual concentration time plots by treatment (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each treatment, with a line for each participant per scale). Plots for ortho-hydroxyatorvastatin and 1-OH-midazolam will be produced separately.
- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time post-dose. Two plots for each participant and scale will be presented: one for ortho-hydroxyatorvastatin and one for the three treatments with 1-OH-midazolam.

The nominal PK sampling time will be used for summary statistics and relevant median plots, whereas for individual participant plots by time, the actual PK sampling time will be used.

6.3.1.4. Biomarkers of CYP3A Induction (Optional)

Plasma 4-β-hydroxycholesterol, cholesterol and EV concentrations for participants in the PK Concentration Set (as defined in Section 4) will be summarized by treatment (i.e. pre-dose at Day 1 in Periods 2, 5, and 8) as outlined in Section 5.2.2.

Absolute values and percent change from baseline in plasma ratios of 4-β-hydroxycholesterol/cholesterol will also be summarized descriptively by treatment as outlined in Section 5.2.2.

The following plots will be presented:

- Box and whisker plots for the absolute values and percent change from baseline in the plasma ratio above will be presented by treatment and overlaid with individual data points.

6.3.2. Part B

6.3.2.1. Additional plasma PK Parameters for LE and EE

C_{max}, T_{max}, CL/F, Vz/F, $t_{½}$* for LE and EE alone and co-administered with PF-06882961 will be listed, summarized descriptively and analyzed by treatment for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

C_{max}, T_{max}, CL/F, Vz/F, $t_{½}$* will be summarized for each treatment (LE and EE will be reported in separate tables) as specified in Table 15.

Table 15. Summary statistics for additional plasma PK parameters for LE and EE

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

*if data permits.

Natural log-transformed C_{max} of LE administered alone or co-administered with PF-06882961 will be analyzed using a mixed effects model as described in Section 5.2.4, using the same approach as outlined in Section 6.1.2.1 for AUC_{inf} and AUC_{last}. The same mixed effects analysis will also be performed for natural log-transformed C_{max} of EE.

The following plots will be presented:

- Box and whisker plots for individual C_{max} values will be presented by treatment and overlaid with geometric means and individual datapoints. These will be produced for LE and EE PK parameters separately.

The following summaries will additionally be presented for the plasma concentration data of LE and EE (reported in separate tables) using the PK Concentration Set (as defined in Section 4):

- A listing of all concentrations sorted by participant ID and nominal time post-dose for each treatment and analyte (i.e. LE or EE) separately. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by each nominal time post-dose (produced separately for each treatment and 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.
- Median concentration time plots (on both linear and semi-log scales) against nominal time post-dose by treatment. Two plots will be presented for each scale: one with LE concentrations for the 3 treatments with OC and one with EE concentrations for the 3 treatments with OC.
- Individual concentration time plots by treatment (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each treatment,

with a line for each participant per scale). Plots for LE and EE will be produced separately.
- Individual concentration time plots by participant (on both linear and semi-log scales) against actual time post-dose. Two plots for each participant and scale will be presented: one with LE concentrations for the 3 treatments with OC and one with EE concentrations for the 3 treatments with OC.

The nominal PK sampling time will be used for summary statistics and relevant median plots, whereas for individual participant plots by time, the actual PK sampling time will be used.

6.3.2.2. Plasma PK Parameters for PF-06882961

Summary of PF-06882961 PK parameters in Part B of the study will be calculated and presented similar as in Part A (Section 6.3.1.2).

6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographics data (age, biological sex, race, ethnicity, body weight, body mass index and height) will be summarized by Part and overall across all participants in the safety population (as defined in Section 4), as described in Sections 5.2.2 or 5.2.3 (as appropriate).

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show end of study participant disposition by treatment and overall and will show which participants were analyzed for PK and safety, which may not be produced in one table. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment. Separate tables will be created for Part A and Part B.

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 separate listings for Part A and Part B.

6.5.4. Other Screening Data

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. Safety Summaries and Analyses

See Section 6.2.

7. INTERIM ANALYSES

7.1. Introduction

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, facilitating PK modeling, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not Applicable.

8. REFERENCES

[1] Considerations, Bioavailabilty and Bioequivalence Studies Submitted in NDAs or INDs - General, *Draft Guidance from the FDA.,* 2014.

9. APPENDICES

Appendix 1. Summary of PK Analyses (Mixed Effects Model)

An example of the PROC MIXED code:

```
proc mixed data=tab.pk;
        class trt subject;
        model &var = trt / ddfm=kr;
        random subject / subject=subject;
        lsmeans trt / diff cl alpha=0.1;
run;
```

Appendix 2. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF:

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

Categories for PR and QRS:

PR (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

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

Appendix 3. C-SSRS Mapped to C-CASA - Suicidal Ideation and Behavior Events and Codes

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	Prepatory actions towards imminent suicidal behaviors	"Yes" on "Prepatory Acts or Behavior"
Self-injurious Behavior, no Sucidial Intent		
1	Self-injurious behavior, no suicidal intent	"Yes" on "Has subject engaged in Nonsuicidal 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".

Appendix 4. List of Abbreviations

Abbreviation	Term
AE	adverse event
AUC	area under the concentration-time curve
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
BPM	beats per minute
C-CASA	Columbia-Classification Algorithm of Suicide Assessment
C-SSRS	Columbia Suicide Severity Rating Scale
CI	confidence interval
CL	clearance
CL/F	apparent oral clearance
C_{max}	maximum observed concentration
CSR	clinical study report
(%)CV	(percent) coefficient of variation
ECG	electrocardiogram
EE	ethinyl estradiol
EV	extracellular vesicles
FU	follow up
HbA1c	hemoglobin A_{1c}
LE	levonorgestrel
LLQ	lower limit of quantification
ln	natural logartihm
MTD	maximum tolerated dose
msec	millisecond
NC	not calculated
ND	not done
NS	no sample
OC	oral contraceptive
PK	pharmacokinetic(s)
PHQ-9	Patient Health Questionnaire-9
PM	post-menopausal
PR	pulse rate
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
SAP	statistical analysis plan
SD	single-dose

Abbreviation	Term
SoA	schedule of activities
$t_{1/2}$	terminal half life
TEAE	treatment emergent adverse event
T_{max}	time to C_{max}
Vz/F	apparent volume of distribution