Protocol C3421007

A PHASE 1, OPEN LABEL, FIXED SEQUENCE STUDY TO EVALUATE THE EFFECT OF TWO STEADY STATE DOSE LEVELS OF PF-06882961 ON THE PHARMACOKINETICS OF SINGLE ORAL DOSES OF ROSUVASTATIN AND MIDAZOLAM IN OTHERWISE HEALTHY ADULT PARTICIPANTS WITH OBESITY

Statistical Analysis Plan
(SAP)

Version: 2.0

Date: 24 May 2021

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

[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 4 Dec 2020	Original 07 Oct 2020	N/A	N/A
2.0 24 May 2021	Original 07 Oct 2020	Updates based on Blinded Data Reviews	Sections 3.2.1 & 3.2.2.3: Updated Baseline 2 definition for labs, vitals, and ECGs CCI [redacted] *Rationale:* to provide a more focused and consistent overview of changes on these parameters during Periods with administration of PF-06882961. Sections 3.2.2 & 6.2.6: Added derivation and summary of the total PHQ-9 score. *Rationale*: need as additional safety parameter for review. CCI [redacted] Section 5.2: Updated treatment labels. *Rationale:* to add additional information on relevant "Period" for added context in tables. Section 6.2.2: Restricted categorical summarization of laboratory abnormalities and vital & ECG values of potential clinical concern to a single baseline definition output. *Rationale:* an additional baseline definition for these outputs was deemed not needed. Sections 6.2.2, 6.2.3 & 6.2.4: Clarified that laboratory abnormalities, vital sign & ECG values of potential concern occurring pre-dose during Periods 2-8, will be attributed

			to the treatment from the previous period. *Rationale:* Tables are presented by treatment (rather than by period) so more appropriately reflects the potential causal relationship. Section 6.2.3: Added plots of absolute mean values over time for vital signs. *Rationale*: providing more comprehensive information on these parameters. Section 6.2.7: Added a listing and summary of the number of participants who met the criteria to be referred to a mental health professional. *Rationale*: table needed for CSR reporting. CCI [redacted]

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3421007. 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***
Primary:	***Primary:***
• *To evaluate the effects of PF-06882961 on the pharmacokinetics of rosuvastatin in otherwise healthy adult participants with obesity.* • *To evaluate the effects of PF-06882961 on the pharmacokinetics of midazolam in otherwise healthy adult participants with obesity.*	• *Rosuvastatin plasma pharmacokinetic parameters: AUC_{inf} (if data permits* otherwise AUC_{last}) in Periods 1, 4 and 7.* • *Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permits* 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 rosuvastatin or midazolam, in otherwise healthy adult participants with obesity.*	• *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 during the entire study.*

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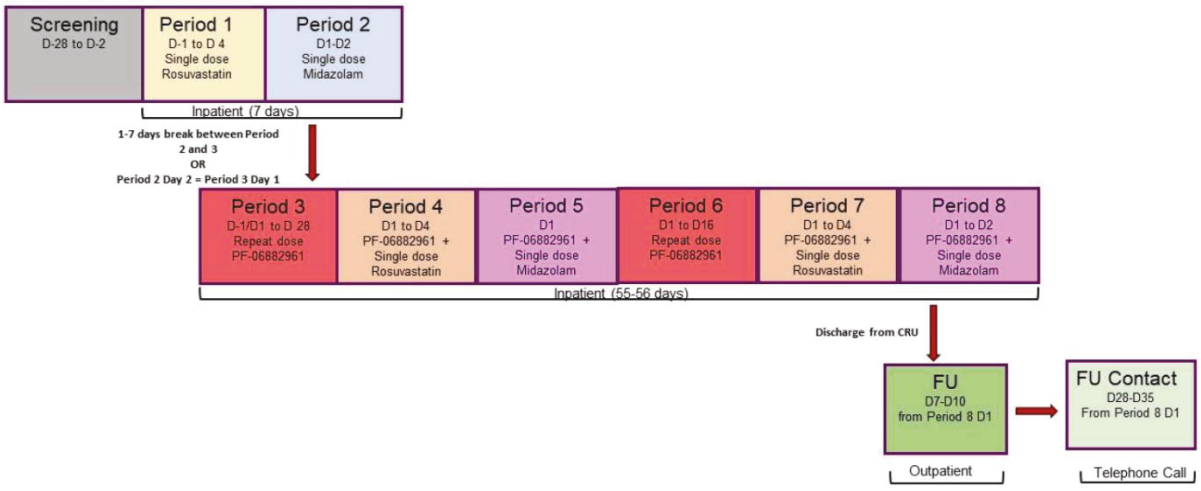
[redacted]	[redacted]
[redacted]	[redacted]
**Should it be deemed that too few AUC_{inf} estimates (e.g. less than 12 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary endpoint for CSR reporting. This will be considered for the rosuvastatin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

There are no estimands for this study.

2.2. Study Design

This study is a Phase 1, open-label, 8-period, fixed-sequence study to evaluate the effect of PF-06882961, administered at two steady-state dose levels, on the pharmacokinetics of rosuvastatin and midazolam, administered separately as single doses, in otherwise healthy adult participants with obesity. A sample size of approximately 16 participants will be enrolled such that approximately 12 evaluable participants complete the study.

Figure 1. Study Design



The total duration of participation from the Screening Visit to the FU contact will be approximately 17 weeks ie, 117 days, of which up to 63 days will be inhouse (Period 1 (rosuvastatin): 5 days, Period 2 (midazolam): 2 days, Period 3 (PF-06882961): 29 days, Period 4 (PF-06882961+rosuvastatin): 4 days, Period 5 (PF-06882961 + midazolam): 1

day, Period 6 (PF-06882961): 16 days, Period 7 (PF-06882961+rosuvastatin): 4 days, Period 8 (PF-06882961 + midazolam): 2 days, FU visit 7-10 days from last dose study intervention and FU contact 28-35 days from last dose study intervention).

Participants may be discharged on Period 2, Day 2 and return to the CRU for Period 3, Day -1 within 7 days from discharge. Alternatively, participants may remain as inpatient on Period 2, Day 2 and begin Period 3, Day 1 activities the same day, without completing Period 3, Day -1 procedures.

Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and Sponsor.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Blood samples for PK analysis of rosuvastatin, midazolam 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)

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

**Should it be deemed that too few AUC_{inf} estimates (e.g. 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 rosuvastatin 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 rosuvastatin and midazolam plasma PK Parameters to be calculated

Parameter	Analysis Scale	Rosuvastatin 10mg (Periods 1, 4 and 7)	Midazolam 2mg (Periods 2, 5 and 8)
AUC_{inf}*	ln	A, D	A, D
AUC_{last}	ln	A, D	A, D

*=if data permits. Abbreviations: A=analyzed using a statistical model; D=displayed with descriptive statistics as outlined in Table 5 in Section 6.1.1; ln=natural-log transformed.

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 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 3. ("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 will not have a change from baseline calculated based on the 2nd definition.

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3.2.2. Assessment of Mental Health

- *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 behaviour. 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 4.

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 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.

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3.4. Baseline Variables

Not applicable.

3.5. Safety Endpoints

See Sections 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 rosuvastatin, midazolam 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 rosuvastatin, midazolam and/or PF-06882961 and have at least 1 of the PK parameters of interest calculated.* *Should vomiting occur after co-administration of rosuvastatin/midazolam 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

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	Rosuvastatin 10 mg (Period 1)
2	Midazolam 2 mg (Period 2)

3	PF-0688291 titration up to 120 mg BID (Period 3)
4	PF-0688291 120 mg BID + rosuvastatin 10 mg (Period 4)
5	PF-0688291 120 mg BID + midazolam 2 mg (Period 5)
6	PF-0688291 titration up to 200 mg BID (Period 6)
7	PF-0688291 200 mg BID + rosuvastatin 10 mg (Period 7)
8	PF-0688291 200 mg BID + midazolam 2 mg (Period 8)

5.2.1. 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.

5.2.2. Analyses for Categorical Endpoints

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

5.2.3. 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 (least squares) mean differences (Test-reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.*

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.

[redacted]

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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 Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of plasma 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. AUC_{inf} and AUC_{last} for midazolam and rosuvastatin

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

Natural log-transformed AUC_{inf} (as data permit) of rosuvastatin administered alone or co-administered with PF-06882961 will be analyzed using a mixed effects model as described in Section 5.2.3. *The two test treatments will be 'Rosuvastatin and PF-06882961 120 mg BID' (Period 4) and 'Rosuvastatin and PF-06882961 200 mg BID' (Period 7), which*

will be reported separately in comparison to the reference treatment of 'Rosuvastatin alone' (Period 1). The same analysis for natural log-transformed AUC_{last} of rosuvastatin will also be conducted.

*Natural log_e-transformed AUC_{inf} (as data permits) of midazolam administered alone or co-administered with PF-06882961 will be analyzed and reported separately using the same mixed effects model as described above for rosuvastatin. The two 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).*The same analysis for natural log-transformed AUC_{last} of midazolam will also be conducted.

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 rosuvastatin 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 rosuvastatin) and 2 (for midazolam) would be included in the models.

AUC_{inf} and AUC_{last} will be summarized for each treatment (rosuvastatin and midazolam will be reported in separate tables) as specified in the table below:

Table 5. Summary statistics to be produced for plasma PK Parameters of rosuvastatin and midazolam

Parameter	Summary Statistics
AUC_{last} & AUC_{inf}	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. These will be produced for rosuvastatin and midazolam PK parameters separately.

In the event that fewer than 12 participants have PK parameters of rosuvastatin and/or midazolam 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 rosuvastatin/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 rosuvastatin, midazolam 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 rosuvastatin and/or midazolam, which would be reported outside of the CSR.

6.2. Secondary Endpoint(s)

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, 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, 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, QTcF interval, 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, 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 5.2.2.

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 separtely by treatment and time point as outlined in Section 5.2.2.

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 5.2.1.

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 5.2.2.

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6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographics data (age, biological sex, race, ethnicity, body weight, body mass index and height) will be summarized across all participants in the safety population (as defined in Section 4) as described in Sections 5.2.1 or 5.2.2 (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.

6.5.3. Concomitant Medications and Nondrug Treatments

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

6.5.4. Other Screening Data

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

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/PD modeling, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1) Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations. *Draft Guidance from the FDA*. March 2014.

[redacted]

[redacted]

9. APPENDICES

Appendix 1. Summary of PK Analyses

Example SAS Code for 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. List of Abbreviations

Abbreviation	Term
AE	adverse event
AUC	area under the curve
BLQ	below the limit of quantitation
BP	blood pressure
CI	confidence interval
CL	clearance
CCI	[redacted]
C-CASA	Columbia-Classification Algorithm of Suicide Assessment
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical study report
CV	Coefficient of variation
ECG	Electrocardiogram
IP	Investigational Product
LLQ	Lower limit of quantitation
ln	Natural log
MTD	maximum tolerated dose
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PK	pharmacokinetic(s)
PHQ-9	Patient Healthy Questionnaire 9
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
SAP	statistical analysis plan
SoA	schedule of activities
T_{max}	Time to maximum observed concentration
CCI	[redacted]

Appendix 4. 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	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*.