Protocol C3421028

AN 8-WEEK, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED PHASE 1 STUDY TO EVALUATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND TOLERABILITY OF PF-06882961 IN CHINESE ADULTS WITH TYPE 2 DIABETES MELLITUS

Statistical Analysis Plan
(SAP)

Version: **2**

Date: 19 Jan 2022

[redacted]

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 03 Feb 2021	Original 10 Dec 2020	N/A	N/A
2 19 Jan 2022	Original 10 Dec 2020	Made some clarifications on variables to be analyzed and added some analyses per team discussion for comparison with other studies within the asset.	• Added descriptions on baseline variables in Section 3.4, especially added variable of "duration of diabetes". • Added description on vital signs and ECG variables in Section 3.5.3 and Section 3.5.4, clarified the baseline definition, description of time-matched changes and added time-matched double difference. • [redacted] • Added summary of treatment compliance in Section 6.5.4. • Added COVID-19 related analyses in Section 6.5.5. • Added some AE analyses in Section 6.6.1. Added the summary of number of TEAEs by severity, SOC and PT. Added the summaries for AEs of interest. • Added analyses for laboratory, vital signs and ECG data in Section 6.6.2, 6.6.3 and 6.6.4. Clarified the summary for time-matched changes and added summary for time-matched double difference. • Added the categories for QTcF in Section 9.1.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3421028. 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

The purpose of this study is to evaluate the PK, safety and tolerability of single and multiple oral doses of PF-06882961 in adult Chinese participants with T2DM who are receiving metformin as background antihyperglycemic medication. The study will be investigator- and participant-blind (sponsor-open), to permit a review of safety and tolerability in order to assess potential for drug-induced changes in participants with T2DM. CCI [redacted]

Objectives , Estimands, and Endpoints:

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To characterize the plasma PK of PF-06882961 following a single oral dose on Day 1 and following multiple, oral doses administered to adult Chinese participants with T2DM.	Not Applicable	• Single dose (10 mg): AUC_{24}, C_{max}. • Multiple dose (40 mg, 80 mg, 120 mg): AUC_{24}, $C_{max,ss}$.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the safety and tolerability of PF-06882961 following a single oral dose on Day 1 and following multiple, oral doses administered to adult Chinese participants with T2DM.	Not Applicable	• Vital signs, Electrocardiograms, Adverse events (e.g. hypoglycemia and hyperglycemia), Clinical safety laboratory assessments.
CCI [redacted]	[redacted]	
[redacted]	[redacted]	[redacted]

[redacted]

2.1.1. Primary Estimand(s)

None.

2.1.2. Secondary Estimand(s)

None.

2.1.3. Additional Estimand(s)

None.

2.2. Study Design

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled, oral dosing study of PF-06882961 in adult Chinese participants with T2DM inadequately controlled on diet, exercise and metformin background therapy.

Participants will receive oral doses of PF-06882961 or placebo in this study. Approximately 20 participants will be randomized to PF-06882961 or placebo at a 3:1 ratio (15 participants

to PF-06882961 and 5 participants to placebo) such that at least 8 participants in PF-06882961 group will complete 120 mg and be evaluable for PK analysis. The study will be conducted at a single clinical site in China.

The target dose level is PF-06882961 120 mg BID (or matching placebo). Following the screening period to confirm eligibility (up to 4 weeks), the treatment period will be approximately 8 weeks, followed by an approximate 4-week follow-up. The dose of PF-06882961 will be increased following a prespecified titration scheme during visits V2 through V8 to reach the target dose, which will then be maintained through V10. Downward titration or dosing is not permitted during the study. Participants who do not tolerate the titration scheme and/or assigned dose may be required to discontinue dosing of study intervention. See **Figure 1** and **Figure 2** for schema of the design and dose titration.

Figure 1. Schema of Study

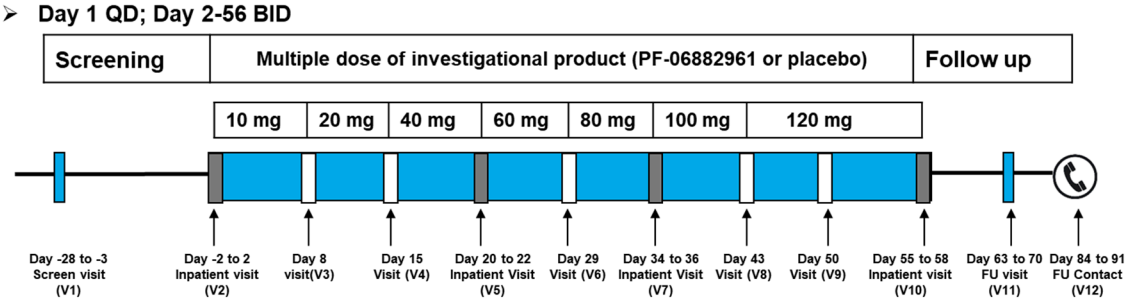
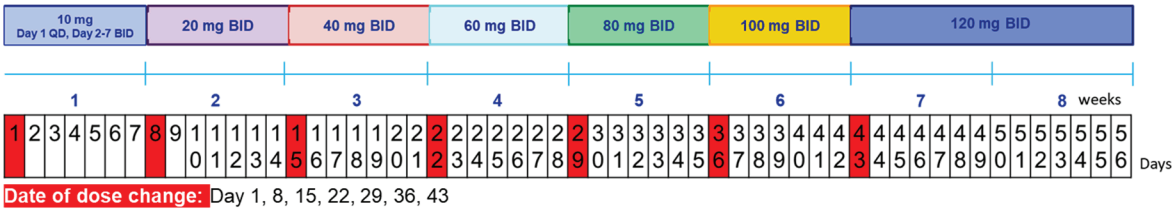


Figure 2. Dose Titration Scheme



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoints of the study are

- Single dose (10 mg): Area under the plasma concentration-time profile from time zero to 24 hours (AUC_{24}), maximum observed concentration observed from time zero to 24 hours (C_{max}) collected at Day 1.
- Multiple dose (40 mg, 80 mg, 120 mg): AUC_{24}, $C_{max,ss}$ collected at steady state.

3.2. Secondary Endpoint(s)

The secondary endpoints of the study are safety endpoints including vital signs, electrocardiograms, adverse events (e.g. hypoglycemia and hyperglycemia), clinical safety laboratory assessments.

More details of the safety endpoint are described in Section 3.5.

CCI [redacted]

The PK parameters (primary endpoints CCI [redacted]) for PF-06882961 will be calculated from the concentration-time data using non-compartmental methods. Definition and method of determination are described in **Table 2** below.

Table 2. Definition of Plasma PK Parameters for PF-06882961

Parameter	Day 1 (D1) or Steady State (SS)	Definition	Method of Determination
C_{max}	D1 & SS	Maximum observed concentration observed from time zero to 24 hours	Observed directly from data
C_{max1} and C_{max2}	D1 & SS	C_{max1}: maximum plasma concentration during the dosing interval τ_1 =0 to 10 hours C_{max2}: maximum plasma concentration during the dosing interval τ_2=10 to 24 hours	Observed directly from data
C_{max1} (dn), C_{max2} (dn) and C_{max} (dn)	D1 & SS	C_{max1}, C_{max2} and C_{max} normalized to a 1 mg dose.	C_{max1}/Dose C_{max2}/Dose C_{max}/Dose
CCI [redacted]	[redacted]	[redacted]	[redacted]
AUC_{tau1} and AUC_{tau2}	SS	Area under the plasma concentration-time profile from time zero to time tau, where tau1 = 0 to 10 hours and tau2 = 10 to 24 hours	Linear/Log trapezoidal method
AUC_{tau1} (dn) and AUC_{tau2} (dn)	SS	AUC_{tau1} and AUC_{tau2} normalized to a 1 mg dose	AUC_{tau1}/Dose AUC_{tau2}/Dose
AUC_{24}	D1	Area under the plasma concentration-time profile from time zero to time 24 hours	Linear/Log trapezoidal method
AUC_{24}	SS	Area under the plasma concentration-time profile from time zero to time 24 hours	AUC_{tau1} + AUC_{tau2}
AUC_{24} (dn)	D1 & SS	AUC_{24} normalized to a 1 mg dose.	AUC_{24}/Total Daily Dose
CCI [redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Table 2. Definition of Plasma PK Parameters for PF-06882961

Parameter	Day 1 (D1) or Steady State (SS)	Definition	Method of Determination
			CCI [redacted]
[redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]			

D1=Day 1. SS=Steady Status. dn= Dose Normalized value.

CCI [redacted]

[redacted]

3.4. Baseline Variables

Baseline variables include age, gender, race, ethnicity, height, weight, body mass index, duration of diabetes, CCI [redacted]. Baseline variables for vital sign and ECG data are described in Section 6.6.3 and Section 6.6.4. Baseline variables are those collected on Day -1 or last measurement during screening visits before Day 1.

The duration of diabetes will the time from primary diagnosis date to the randomization date into this study.

3.5. Safety Endpoints

3.5.1. Adverse Events (AEs)

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment.

All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time will be flagged as TEAEs. If an AE starts on the same day as the first dose date, it will be considered treatment emergent unless the case report form data indicates otherwise via explicitly recording time for AE onset and treatment dosing.

3.5.1.1. Hypoglycemic Adverse Event (HAE)

Details of hypoglycemia AEs will be recorded in the Case Report Form (CRF) as a separate page. The definition and severity of categorization of HAE are described in the protocol Section 8.2.5.2.1.

For programming purposes, the hypoglycemic AE categories are based on the following:

- **Severe Hypoglycemia**: Severe is checked in the severity criteria of the CRF. This assessment will be made by the PI based on the protocol definition.
- **Documented Symptomatic Hypoglycemia**: If (1 – Did the subject have symptoms of hypoglycemia?) Yes and (2 – Was blood glucose measured?) Yes and result <70 mg/dL on the CRF, but hypoglycemia is not classified as severe.
- **Asymptomatic Hypoglycemia**: If (1) No and (2) Yes and result <70 mg/dL on the CRF, but hypoglycemia is not classified as severe.
- **Probable Symptomatic Hypoglycemia**: If (1) Yes and (2) No and (2b – If blood glucose was not measured, did symptoms resolve when treated with carbohydrate or glucagon?) Yes on the CRF, but hypoglycemia is not classified as severe.

3.5.2. Laboratory Data

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

To determine if there are any clinically significant laboratory abnormalities, the hematological, clinical chemistry, urinalysis, and other safety tests will be assessed against the criteria specified in the sponsor reporting standards.

Baseline will be the last predose measurement collected on Day -1.

3.5.2.1. Change form Baseline Summaries

Focused change from baseline summaries of the following safety laboratory endpoints will be assessed:

- Change from baseline in calcitonin to all post-dose time points as per the Schedule of activities (SoA) in the protocol .
- Change from baseline in amylase to all post-dose time points as per the SoA.
- Change from baseline in lipase to all post-dose time points as per the SoA.
- Change from baseline in thyroid stimulating hormone (TSH) to all post-dose time points as per the SoA.
- Change from baseline in free thyroxine (free T4) to all post-dose time points as per the SoA.
- Change from baseline in lipid profile (total cholesterol, direct LDL cholesterol, HDL cholesterol and triglycerides) to all post-dose time points as per the SoA.

- Change from baseline in liver function tests (ALT, AST, alkaline phosphatase, and total bilirubin) to all post-dose time points as per the SoA.

3.5.3. Vital Signs

Vital sign measurements (blood pressure and pulse rate) will be taken as detailed in the schedule of activities given in the protocol. The average of the triplicate measurements at each appropriate assessment time will be calculated for each blood pressure and pulse rate, if applicable.

Changes from time-matched baseline for supine systolic and diastolic blood pressure and pulse rate will be calculated for each post baseline measurement. Baseline is defined as the time-matched value from the average of the triplicate recordings on Day -1.

In addition, the time-matched double difference in supine blood pressures and pulse rate measurements is calculated in the following steps: (1) subtract predose value on Day 1 from all postdose values; (2) subtract the value at 0 hours on Day -1 from all other values on Day -1; (3) take the difference between the adjusted postdose value in (1) and its time-matched value in (2).

3.5.4. Electrocardiograms

Standard 12-lead ECG (including heart rate, PR, QT, QTcF intervals and QRS complex) will be obtained at times detailed in the schedule of activities given in the protocol. The average of the triplicate readings collected at each appropriate assessment time will be calculated for each ECG parameter, if applicable.

Change from time-matched baseline for heart rate, PR, QT, QTcF intervals and QRS complex will be calculated for each post baseline measurement. Baseline is defined as the time-matched value from the average of the triplicate recordings on Day -1.

In addition, the time-matched double difference in heart rate, PR, QT, QTcF and QRS measures is calculated in the following steps: (1) subtract predose value on Day 1 from all postdose values; (2) subtract the value at 0 hours on Day -1 from all other values on Day -1; (3) take the difference between the adjusted postdose value in (1) and its time-matched value in (2).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative'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.

Defined Analysis Set	Description
PK Concentration Analysis Set	It is defined as all participants randomized and treated with PF-06882961 who have at least 1 plasma concentration value collected. The PK concentration analysis set will be used for plasma concentration summaries and plots.
PK Parameter Analysis Set	It is defined as all participants randomized and treated with PF-06882961 who have at least 1 of the PK parameters of interest. The PK parameter analysis set will be used for analyses on the PK parameters.
CCI [redacted]	[redacted]
Safety Analysis Set (SAS)	It is defined as all participants who are randomized and receive at least one dose of study medications. The safety population will be used for the safety analyses.

Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from participants who are randomized but not treated.

If a participant takes a treatment that is not consistent with the treatment they are randomized to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety and PK analyses, where applicable.

Protocol Deviations

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

A full list of protocol deviations will be compiled and reviewed to identify potential important deviations and COVID-19 related deviations (if any) prior to database closure.

5. GENERAL METHODOLOGY AND CONVENTIONS

The study data will be analyzed following the database release once all paricipants have completed the study (or discontinued from study).

5.1. Hypotheses and Decision Rules

None.

5.2. General Methods

In general, PF-06882961 plasma PK concentration and parameters data will be summarized descriptively for single dose and multiple doses separately; safety endpoints will be summarized by treatment group and dose levels; CCI [redacted]

5.2.1. Analyses for PK Concentration and Parameters

Concentration data will be listed and summarized descriptively by PK sampling time and day (dose level). Summary profiles (mean and median) of the plasma concentration-time data will be plotted by day (dose level) against nominal PK sampling time. Mean and median profiles will be presented on both linear-linear and loglinear scales. Spaghetti plots of individual plasma concentration-time data will be plotted by day (dose level) and actual PK sampling time.

The primary endpoints AUC_{24}, C_{max}, $C_{max,ss}$, CCI [redacted] will be summarized descriptively with n, arithmetic mean, standard deviation, coefficient of variatiation (CV%), geometric mean, geometric CV (%), median, minimum, and maximum. Box and whisker plot of individual and geometric mean will be presented for dose normalized AUC_{24}, C_{max}, $C_{max,ss}$.

5.2.2. Analyses for Continuous Endpoints

Continous endpoints will be summarized descriptively by treatment, dose level and day (if collected multiple days for same dose level) with summary statistics of n, mean, standard deviation, median, minimum, and maximum.

CCI [redacted]

CCI [redacted]

CCI [redacted]

5.2.3. Analyses for Categorical Endpoints

Categorical endpoints will be summarized descriptively by treatment, dose level and day (if collected multiple days for same dose level) with n, number of observed values, and percentages.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the CDISC and Pfizer Standard (CaPS) rules for imputation will be applied.

5.3.1. Concentrations Below the Limit of Quantification

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

5.3.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

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

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

5.3.3. Pharmacokinetic Parameters

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

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

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

If an individual participant has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

CCI [redacted]

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

The primary endpoints, AUC_{24} (Day 1 and Steady State), C_{max} (D1), $C_{max,ss}$, will be summarized descriptively as described in Section 5.2.1.

In addition, to support the assessment of primary endpoints, AUC_{tau1} (Steady State), AUC_{tau2} (Steady State), C_{max1} (Steady State), C_{max2} (Steady State), AUC_{tau1}(dn) (Steady State), AUC_{tau2}(dn) (Steady State), AUC_{24}(dn) (Day 1 and Steady State), C_{max1}(dn), C_{max2}(dn), C_{max} (dn), $C_{max,ss}$ (dn) will also be summarized descriptively. Box and whisker plots will be generated for AUC_{24} (dn) (Day 1 and Steady State), C_{max}(dn)(D1), $C_{max,ss}$(dn). See **Table 3**.

The PK parameter analysis set will be used for the aforementioned summaries and plots.

Table 3. Descriptive Summris for Primary PK Parameters Following the Single Dose/Multiple Doses

Summarized by Dose Level	
Parameter	**Summary Statistics**
AUC_{24} (D1 and SS), C_{max} (D1), $C_{max,ss}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
AUC_{tau1} (SS), AUC_{tau2} (SS), C_{max1} (SS), C_{max2} (SS)	
AUC_{tau1} (dn) (SS), AUC_{tau2} (dn) (SS), AUC_{24} (dn) (D1 and SS), C_{max1} (dn) (SS), C_{max2} (dn) (SS), C_{max} (dn) (D1), $C_{max,ss}$ (dn)	

D1=Day 1. SS=Steady Status. dn= Dose Normalized value. cv=Coefficient of Variation.

Presentations for PF-06882961 concentrations will be generated for the single dose and multiple doses separately, including:

- A listing of all concentrations sorted by participant ID and nominal time postdose, and page by dose level for multiple dosing days. 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 dose level and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, cv, minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by dose levels (all dose levels on the same plot per scale for multiple dosing days) based on the summary of concentrations by dose level and nominal time postdose.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by dose levels (all dose levels on the same plot per scale for multiple dosing days) based on the summary of concentrations by dose level and nominal time postdose.

- Individual concentration time plots by by dose (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for the single dose and each multiple dose level per scale).

- Individual concentration time plots by participant (on both linear and semi-log scales) and dose level against actual time postdose (there will be separate plots for each participant on single dose, and separate plots for each participant with all dose levels on the same plot per scale).

For summary statistics and median/mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used. The PK concentration analysis set will be used for all the concentration data summaries and plots.

6.2. Secondary Endpoint(s)

The secondary safety endpoints will be summarized using the safety analysis set as described in Sections 5.2.2 and 5.2.3, and analyses for each safety endpoint are described in Section 6.6.

CCI [redacted]

[redacted]

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

[redacted]

[redacted]

[redacted]

6.4. Subset Analyses

None.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographic and baseline characteristics (age, gender, race, ethnicity, weight, height, body mass index and duration of diabetes) collected prior to the first dose of the study intervention will be summarized by treatment group following the CaPS.

6.5.2. Study Conduct and Participant Disposition

Participant disposition will be reported by showing the number (and percent) of participants completed study, discontinued from studies, as well as the number (and percent) of participants analyzed for each analysis set by treatment group.

6.5.3. Concomitant Medications and Nondrug Treatments

All concomitant medications as well as nondrug treatments will be provided in the listings.

A separate listing restricted to metformin will also be produced.

6.5.4. Treatment Compliance

A summary table of treatment compliance will be produced by study week according to current sponsor reporting standards.

"Study Week" will be calculated using actual visit dates per dose titration dates, rather than the calendar days. For example, if dose missing occurs on Day 8 and dose titration occurs on Day 9 for a given patient, then the dose missing is considered to have occurred on Week 1 for this patient (Week 1 is Day1 to Day 8 for this patient).

6.5.5. COVID-19 Related Analyses

Considering the small sample size in this study, no separate summary tables are planned for COVID-19 related analyses. Only some key listings will be previded. e.g.,

Protocol Deviations related to COVID-19,

Subject Discontinuations Related to COVID-19,

COVID-19 related Adverse Events.

6.6. Safety Summaries and Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to the CaPS.

6.6.1. Adverse Events

Adverse events will be reported in accordance with the CaPS by treatment group and dose level.

Besides the standard incidence and severity of TEAE summaries, the number of TEAEs (all causality and treatment related) by severity, System Organ Class, and Preferred Term will also be produced.

The hypoglycemic AEs will be listed in a separate table and summarized categorically (See Section 3.5.1.1) by treatment and dose level.

CCI [redacted]

CCI [redacted]

[redacted]

6.6.2. Laboratory Data

Incidence of laboratory test (including hematological, clinical chemistry, urinalysis tests) abnormalities (without regard to baseline abnormality, with normal baseline and abnormal baseline respectively) will be reported.

Baseline value and CFB for the laboratory tests of interest listed in Section 3.5.2.1 will be summarized descriptively via the method stated in Section 5.2.2.

6.6.3. Vital Signs Data

Baseline values, absolute values and changes from time-matched baseline values in supine systolic, supine diastolic blood pressure and pulse rate will be summarized by treatment, time post-dose and day with descriptive statistics stated in Section 5.2.2 (according to CaPS). Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

Maximum absolute values and maximum changes from time-matched baseline for vital signs will also be summarized descriptively as stated in Section 5.2.3 using categories as defined in Appendix 1 (Section 9.1).

All planned and unplanned post dose time points will be counted in these categorical summaries.The time-matched double differences in vital signs obtained following the Day 1 treatment, as defined in Section 3.5.3, will be summarized (N, mean, 90% confidence interval) for each treatment and time point.

Mean time-matched double differences in vital signs will be plotted against time post-dose for Day 1 and Day 56 separately. On each plot there will be 1 line for each treatment.

6.6.4. ECG Data

Baseline values, absolute values and changes from time-matched baseline in QT, heart rate, QTcF interval, PR interval and QRS complex will be summarized by treatment and time post-dose and day with descriptive statistics stated in Section 5.2.2 following CaPS. Tables will be paged by parameter. Baseline is as defined in Section 3.5.4.

Maximum increase from time-matched baseline for QTcF and heart rate will be summarized by treatment, according to sponsor reporting standards.

The number (%) of participants with maximum absolute value and maximum increase from baseline for QTcF, PR and QRS (see Appendix 1 in Section 9.1) will be summarized using method stated in Section 5.2.3.

All planned and unplanned post-dose time-points will be counted in these categorical summaries.

The time-matched double differences in QT interval, heart rate, QTcF interval, PR interval, and QRS complex measures obtained following the Day 1 treatment, as defined in Section 3.5.4, will be summarized (N, mean, 90% confidence interval) for each treatment and time point.

6.6.5. Mean time-matched double differences in ECG parameters will be plotted against time postdose for Day 1 and Day 56 separately. On each plot there will be 1 line for each treatment. Physical Examination

Physical examinations will be summarized by treatment and dose level in accordance to CaPS.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study.

7.1. Introduction

None.

7.2. Interim Analyses and Summaries

None.

8. REFERENCES

None.

9. APPENDICES

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

Categories for QTcF

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	450 < QTcF <= 480	480 < QTcF <= 500	>500
Increase from baseline		30 < Increase <= 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

BP: blood pressure.

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

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.3. List of Abbreviations

Abbreviation	Term
%CV	coefficient of variation, percent
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CCI [redacted]	[redacted]
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{tau}	area under the concentration-time curve at steady state over the dosing interval τ
BID	twice daily
BLQ	below the limit of quantification
BP	Blood pressure
CaPS	CDISC and Pfizer Standard
CDISC	clinical data interchange standards consortium
CCI [redacted]	[redacted]
CFB	change from baseline
CCI [redacted]	[redacted]
C_{max}	maximum observed concentration

[redacted]

[redacted]

Abbreviation	Term
$C_{max,ss}$	maximum observed concentration, steady state
CCI	[redacted]
COVID	coronavirus disease
CRF	case report form
CCI	[redacted]
dn	dose normalized
ECG	electrocardiogram
CCI	[redacted]
HAE	hypoglycemic adverse event
CCI	[redacted]
HDL	high-density lipopritein
CCI	[redacted]
LDL	lower-density lipoprotein
LLQ	lower limit of quantification
CCI	[redacted]
CCI	[redacted]
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
CCI	[redacted]
PK	pharmacokinetic(s)
CCI	[redacted]
QRS	time from ECG Q wave to the end of the S wave corresponding to ventricle depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
SAP	statistical analysis plan
SAS	safety analysis set
SoA	Schedule of Activies
SS	steady-state
CCI	[redacted]
T2DM	type 2 diabetes mellitus
TEAE	Treatment emergent adverse event
CCI	[redacted]
TSH	thyroid stimulating hormone
CCI	[redacted]
CCI	[redacted]