Protocol C3421015

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

Statistical Analysis Plan
(SAP)

Version: **2**

Date: 06-Apr-2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 21 Aug 2020	Original 30 Jun 2020	N/A	N/A
2 06 Apr 2021	Original 30 Jun 2020	CCI [redacted]	[redacted]
		CCI [redacted]	[redacted]
		CCI [redacted]	[redacted]
		Updated the analysis based on the blinded data review	Delete the recurrence analysis from Section 6.1.1.2.
		Clarified the details	Add the following sentences in Section 6.1.1.3. To calculate the percentage each week, the total number of participants who had not discontinued from the treatment prior to that respective week will be the denominator (note: if a participant did discontinue from the treatment during that respective week, they would be included in the denominator).

			"Study Week" will be calculated using actual visit dates, rather than calendar days. For example, if vomiting occurs on Day 8 and Visit 2 occurs on Day 9 for a given patient, then the vomiting is considered to have occurred on Week 1 for this patient (Week 1 is Day1 to Day 8 for this patient).
		CCI [redacted]	[redacted]
		Clarified the details	Add the following sentence in Section 6.5.5. "Study Week" will be calculated using actual visit dates, rather than calendar days. For example, if vomiting occurs on Day 8 and Visit 2 occurs on Day 9 for a given patient, then the vomiting is considered to have occurred on Week 1 for this patient (Week 1 is Day1 to Day 8 for this patient).

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3421015. 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

There are no estimands in this study. Analysis population and methods to manage missing data are shown in Section 4 and Section 5.3, respectively.

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of multiple, oral doses of PF-06882961, administered to adult Japanese participants with T2DM.	• Incidence of treatment emergent AEs (AEs and SAEs), clinical laboratory abnormalities, vital signs and ECG parameters during the entire study.

Secondary: • To characterize plasma pharmacokinetics of PF-06882961 following Day 1 and following multiple, oral doses administered to adult Japanese participants with T2DM.	**Secondary:** • PF-06882961 plasma pharmacokinetic parameters AUC_{24}, C_{max}, T_{max}, $t_{½}$ (as defined in Section 9.4.3.1 in the protocol, as appropriate for the dosing paradigm) following Day 1, and multiple dose administration, as data permit.
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[redacted]	[redacted]
[redacted]	[redacted]

2.2. Study Design

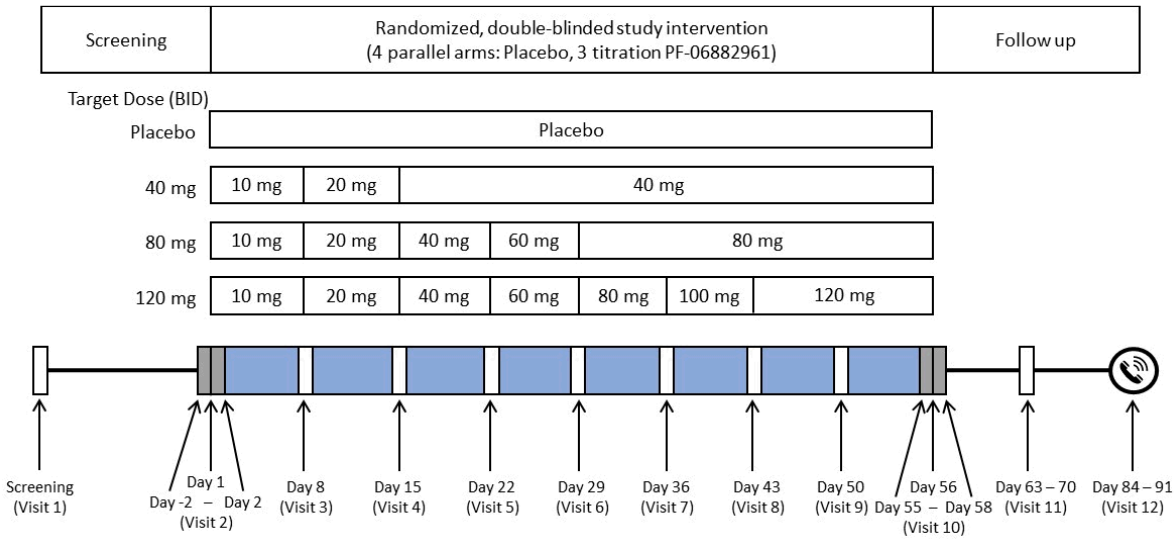
This is a Phase 1, randomized, double-blind (sponsor-open), placebo-controlled, 4-arm, parallel group study of PF-06882961 in adult Japanese participants with T2DM inadequately controlled on diet and exercise alone.

Participants will receive oral doses of PF-06882961 or placebo in this study. Approximately 9 participants will be enrolled in each arm, for a total of approximately 36 (4 arms) participants randomized. The randomization ratio will be 1:1:1:1 (1 of 3 active dosing regimens of PF-06882961 or placebo), and all 4 arms will be enrolled in parallel. The study will be conducted at a single clinical site in Japan.

Target dose levels, achieved after completion of titration, for the 4 arms of the study are placebo and PF-06882961 doses of 40 mg BID, 80 mg BID, and 120 mg BID. Dose titration will be incorporated to enhance tolerability to PF-06882961.

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.

Figure 1. Schema of Study C3421015



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Incidence of treatment emergent AEs (AEs and SAEs), clinical laboratory abnormalities, vital signs and ECG parameters during the entire study.

3.1.1. Adverse Events

An adverse event is considered treatment emergent (TEAE) relative to a given treatment if:

- The event starts during the effective duration of treatment (i.e. starting after the first dose but before the last dose plus lag time)

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time, whether this occurs during a break in treatment or at the end of treatment, is attributed to the corresponding treatment period. The lag time is defined by the Pfizer Standard of 365 days post last dose of study intervention.

A 3-tier approach will not be used to summarize TEAEs due to small sample size.

3.1.1.1. Hypoglycemia Monitoring

Hypoglycemia AEs will be recorded in the Case Report Form (CRF) as a separate page. Details of when these will be recorded are given in the protocol Section 8.2.5.2.

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 principal investigator based on the protocol definition.
- Documented Symptomatic Hypoglycemia: If (2 – Did the subject have symptoms of hypoglycemia?) Yes and (3 – Was blood glucose measured?) Yes and result <70 mg/dL (3.9 mmol/L) on the CRF, but hypoglycemia is not classified as severe.
- Asymptomatic Hypoglycemia: If (2) No and (3) Yes and result <70 mg/dL (3.9 mmol/L) on the CRF, but hypoglycemia is not classified as severe.
- Probable Symptomatic Hypoglycemia: If (2) Yes and (3) No and (3a – 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.

3.1.2. 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, QT, QTcF, PR 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).

3.1.3. 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).

3.1.4. Laboratory Data

Safety laboratory tests (hematology, chemistry, urine testing and other clinical laboratory tests) will be performed as described in the protocol（Table 2）.

To determine if there are any clinically significant laboratory abnormalities, the safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline for all laboratory measurements will be defined as the Day -1, 0H time point for each measure.

Table 2. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine eGFR **Plasma** glucose Calcium Sodium Potassium Chloride AST ALT Total bilirubin GGT Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a] Urine pregnancy test	Lipid panel: ● Total cholesterol ● Direct LDL-C ● HDL-C ● Triglycerides TSH Free T4 Calcitonin Amylase Lipase **Serum** total bile acids PT/INR/aPTT Serum pregnancy test (β-hCG) <u>At screening and/or Day-2 only:</u> • FSH[b] • Urine drug screening[c] • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody • Human immunodeficiency virus • Syphilis
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT (repeat) PT/INR (repeat) Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).

3.2. Secondary Endpoint(s)

3.2.1. Pharmacokinetic Endpoints as Secondary Endpoint

Blood samples for PK analysis of PF-06882961 will be taken according to the schedule of activities given in the protocol.

PK parameters for plasma PF-06882961 following single and multiple dose administration of PF-06882961 will be derived using standard noncompartmental methods, as data permit for each treatment and Day [Day 1 and Day 56], from the concentration time profiles in the table as follows:

Table 3. Pharmacokinetic Endpoints as Secondary Endpoint

Parameter	Definition	Method of Determination	Analysis
Plasma Parameters			
C_{max}	Maximum plasma concentration observed from time zero to 24 hours	Observed directly from data	ln, D
C_{max1}	C_{max1}: maximum plasma concentration during the dosing interval τ_1 =0 to 10 hours	Observed directly from data	ln, D
C_{max2}	C_{max2}: maximum plasma concentration during the dosing interval τ_2=10 to 24 hours	Observed directly from data	ln, D
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence	R, D
T_{max1}	Time for C_{max1}	Observed directly from data as time of first occurrence	R, D
T_{max2}	Time for C_{max2}	Observed directly from data as time of first occurrence	R, D
AUC_{24}	Area under the plasma concentration-time profile from time zero to time 24 hours	$AUC_{\tau1}$ +$AUC_{\tau2}$	ln, D
$t_{1/2}$*	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.	R, D

Key: D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=not calculated at Day 1.

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3.4. Baseline Variables

Full details on the covariates to be included in analyses are given in Section 5.2.4 and Section 5.2.5.

Baseline variables are age, gender, race, ethnicity, height, weight, body mass index, duration of diabetes, [redacted] eGFR, systolic blood pressure, and diastolic blood pressure. Baseline variables are those collected on Day 1 prior to dosing or last measurement during screening visits before Day 1.

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.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK concentration	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and in whom at least 1 plasma PK concentration value is reported.
PK parameter	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and who have at least 1 of the PK parameters of interest calculated.
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4.1. Treatment Misallocations

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

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

4.2. Protocol Deviations

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

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

4.2.1. Deviations Assessed Prior to Randomization

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

4.2.2. Deviations Assessed Post-Randomization

Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No formal inferential statistics will be applied to the safety, PK CCI data.

5.2. General Methods

All treatment arms of PF-06882961 and placebo will be reported separately.

5.2.1. Analyses for Continuous Endpoints

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

5.2.2. Analyses for Categorical Endpoints

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

5.2.3. Anlayises of Time to event Endpoints

A Kaplan-Meier curve will be produced based on the time to the event of interest (starting from the time of start of dosing on Day 1) for each treatment separately and will be plotted on the same graph. No statistical testing for differences between treatment will be considered.

Details of censoring are included in Section 6.1.1.2.

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5.3. Methods to Manage Missing Data

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

5.3.1. Concentrations Below the Limit of Quantification

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

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 subject discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

If a subject receives a dose that was not assigned based on the randomized titration scheme, the data from that Day will not be included in any summary statistics but will be included in listings.

If an individual subject 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.

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6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Adverse events

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

Incidence and severity of treatment emergent adverse event (TEAE) tables will additionally be produced ('All causality' and 'Treatment related', separately) to summarise the total number of adverse events by preferred term, which will be reported by treatment group (Placebo, 40 mg BID, 80 mg BID and 120 mg BID) and overall.

6.1.1.1. Hypoglycemia Monitoring

The hypoglycemic AEs will be listed in a separate table and summarized categorically by treatment as per Section 5.2.2.

6.1.1.2. Time to First Occurrence of AEs of Interest

Exploratory summaries on the time to the first occurrence of AEs of interest will be produced using Kaplan-Meier (KM) Curves as described in Section 5.2.3. Participants who discontinue from the study, discontinue from IP or initiate glycemic rescue medication prior to the start of the AE event of interest will be censored at the discontinuation/initiation date.

The three AEs of interest are: diarrhea, nausea and vomiting (based on preferred term). A separate KM plot for each AE will be produced separately.

Listings of AEs of interest will be produced.

6.1.1.3. Percentage of Participants with Ongoing AEs of Interest

Exploratory summaries on the percentage of participants reporting AEs of interest will be produced by week and treatment as per Section 5.2.2.

A line plot of the percentages over each week will be produced based on the summary statistics with a separate line for each treatment.

The AEs of interest are diarrhea, nausea and vomiting (based on preferred term); where a separate table and plot will be produced for each AE.

To calculate the percentage each week, the total number of participants who had not discontinued from the treatment prior to that respective week will be the denominator (note: if a participant did discontinue from the treatment during that respective week, they would be included in the denominator).

"Study Week" will be calculated using actual visit dates, rather than calendar days. For example, if vomiting occurs on Day 8 and Visit 2 occurs on Day 9 for a given patient, then the vomiting is considered to have occurred on Week 1 for this patient (Week 1 is Day1 to Day 8 for this patient).

6.1.2. Electrocardiograms

Absolute values and changes from time-matched baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.1.2.

Mean change from time-matched baseline in ECG parameters will be plotted against day (for Day 1 and Day 56). On each plot there will be 1 line for each treatment. Corresponding individual plots of change from time-matched baseline will also be produced for each treatment.

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

ECG endpoints and change from time matched baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using the following categories. 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.

Table 5. Categories for QTcF Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

Table 6. Categories for PR and QRS Assessment

Parameter	Criteria	
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	

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

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 3.1.2, will be summarized (N, mean, 90% confidence interval) for each treatment and time point.

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 and a single line for the placebo group(s). Corresponding individual plots of time-matched double differences will also be produced for each treatment.

The time matched double differences in QTcF will be plotted against PF-06882961 concentration. This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Placebo data will also be included (with drug concentration set to zero). Different symbols will be used for each treatment.

6.1.3. Vital Signs

Absolute values and change from time-matched baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment, time post-dose and day, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.1.3.

Mean change from time-matched baseline for supine systolic and diastolic blood pressure and pulse rate will be plotted against time post-dose and day. On each plot there will be 1 line for each treatment. Corresponding individual plots of change from time-matched baseline will also be produced for each treatment.

Maximum absolute values and change from time-matched baseline for vital signs will also be summarized descriptively by treatment using the following categories. Numbers and percentages of subjects 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.

Table 7. Categories for Vital Signs

Parameter	Criteria	
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

The time-matched double differences in vital signs obtained following the Day 1 treatment, as defined in Section 3.1.3, 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. Corresponding individual plots of time-matched double differences will also be produced for each treatment.

6.1.4. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.1.4.

6.2. Secondary Endpoint(s)

6.2.1. Pharmacokinetic Endpoints as Secondary Endpoint

The PK parameters detailed in Section 3.2.1 will be listed and summarized for subjects in the PK parameter analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.3. Each PK parameter will be summarized descriptively by treatment, dose and day (Day 1 and Day 56) as detailed in Section 3.2.1.

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

Table 8. PK Parameters to be Summarized Descriptively

Parameter	Matrix	Summary Statistics
C_{max}, C_{max1}, C_{max2}, AUC_{24}	Plasma	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum, geometric mean and geometric CV%.
T_{max}, T_{max1}, T_{max2}	Plasma	N, median, minimum, maximum.
$t_{1/2}$*	Plasma	N, arithmetic mean, median, CV%, standard deviation, minimum, maximum.

*=not calculated at Day 1.

There will be one summary table for all PK parameters. The treatment subheading will include the matrix, dose information and day. As per Section 5.3.3, data collected on days that subjects received anything other than the assigned dose based on the titration scheme will only be listed and not summarized as part of the summary table.

Supporting data from the estimation of t½ will be listed where applicable: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); 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.

No formal inferential statistics will be applied to the PK data.

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6.4. Subset Analyses

No subset analysis will be conducted for this study.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Baseline data (age, gender, race, ethnicity, height, weight, body mass index, duration of diabetes, [redacted] systolic blood pressure, and diastolic blood pressure) will be summarized by treatment and overall.

6.5.2. Study Conduct and Participant Disposition

The following participant dispositions will be summarized.

- A summary of participant discontinuations up to end of study;
- Summary of participant dispositions analyzed for PK[redacted] as well as for safety;
- Summary of numbers of participant treated by treatment group.

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

6.5.3. Concomitant Medications and Nondrug Treatments

All concomitant medications as well as nondrug treatments will be summarized in accordance with the sponsor reporting standards.

6.5.4. Medical History

All medical histories will be summarized in accordance with the sponsor reporting standards.

6.5.5. Treatment Compliance

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

"Study Week" will be calculated using actual visit dates, rather than calendar days. For example, if vomiting occurs on Day 8 and Visit 2 occurs on Day 9 for a given patient, then the vomiting is considered to have occurred on Week 1 for this patient (Week 1 is Day1 to Day 8 for this patient).

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7. INTERIM ANALYSES

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

8. REFERENCES

[1] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412-419.