Protocol C3991003

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE ORAL DOSES OF PF-07081532 IN ADULT PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS

Statistical Analysis Plan (SAP)

Version: 2

Date: 29 Jul 2022

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

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 14th Jan 2022	N/A	• Original protocol	N/A
2 28th Jul 2022	N/A	• Based on data review before database release, SQE (#PR2205605) was opened regarding confirmed aberrant glucose values reported by the site. SAP amendment is supported by DMB02 SOP and QMS-01 SOP	Impacted sections of SAP V1: Section 3.3.1: reference to glucose AUC_{0-4} removed Section 3.3.4 - Change from baseline in MDG - removed Section 5.3.5: reference to glucose AUC_{0-4} and AUC_{24} removed Section 6.3.1: reference to glucose AUC_{0-4} removed Section 6.3.4: entire section removed
		• Repeated wording for summarization of change from baseline on safety laboratories	Section 3.4.1.2 removed
		• Listings of laboratory parameter of interest should only be listed/ Alignment with C3991002 outputs using Pfizer standards for reporting	Section 6.7.1: Focused Laboratory Summaries on Endpoints of Interest removed
		• Physical examination data is not collected in this study	Section 6.7.2: Entire section removed

2. INTRODUCTION

This statistical analysis plan amendment (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3991003 issued on September, 21st 2021.

2.1. Modifications to the Analysis Plan Described in the Protocol

The following endpoints

- *The MDG will be computed by AUC_{24}/24 hour.*
- *The $AUC_{(0-4)}$ for glucose will also be calculated.*

as described in Section 9.3.4 of the protocol has been removed due to aberrant glucose values (see Version History).

2.2. Study Objectives, Endpoints, and Estimands

Objectives	***Endpoints***
Primary:	***Primary:***
• *To evaluate the safety and tolerability of multiple doses of PF-07081532, administered orally, in adult participants with inadequately controlled T2DM on metformin and if enrolled, in non-diabetic participants with obesity.*	• *Assessment of AEs, safety laboratory tests, vital signs and 12-lead ECGs.*
Secondary:	***Secondary:***
• *To characterize plasma PK of PF-07081532 following multiple doses administered orally, in adult participants with inadequately controlled T2DM on metformin and if enrolled, in non-diabetic participants with obesity.*	• *PF-07081532 plasma PK parameters AUC_{24}, C_{max}, T_{max} on Day 1 and Day 42 and $t_{½}$ on Day 42, as data permit.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
• *To characterize the PD effect on glucose, insulin, glucagon, and C-peptide excursions after a MMTT following multiple doses of PF-07081532, administered orally, in adult participants with inadequately controlled T2DM on metformin.*	• *CFB in response to MMTT at all postdose timepoints as specified in the SoA for $AUC_{(0-4)}$ for glucose, insulin, glucagon, and C-peptide.*
• *To explore the PD effect on MDG*, HbA1c*, plasma glucose, plasma insulin, and HOMA-IR following multiple doses of PF-07081532, administered orally, in adult participants with T2DM inadequately controlled on metformin and, if enrolled, in non-diabetic participants with obesity.*	• *CFB at all post-dose timepoints as specified in the SoA for:* o *Fasting plasma glucose;* o *Fasting plasma insulin;* o *HOMA-IR;* o *HbA1c*;* o *MDG*.*

Objectives	*Endpoints*
• *To assess the PD effect on body weight changes following multiple doses of PF-07081532, administered orally, in adult participants with T2DM inadequately controlled on metformin and if enrolled, in non-diabetic participants with obesity.*	• *CFB in body weight at all post-dose timepoints as specified in the SoA.*
• To further characterize plasma PK of PF-07081532 following multiple doses administered orally, in adult participants with inadequately controlled T2DM on metformin and if enrolled, in non-diabetic participants with obesity.	• Additional PF-07081532 plasma PK parameters following multiple dose administration including, as data permit: AUC_{24}(dn), AUC_{inf}, AUC_{last}, C_{av}, CL/F, C_{max}(dn), C_{min}, R_{ac}, $R_{ac,Cmax}$, PTR, V_z/F

* not analyzed in non-diabetic population with obesity, if enrolled

2.2.1. Primary Estimand(s)

Not applicable because C3991003 is a Phase 1 study with no estimands on safety endpoints

2.2.2. Secondary Estimand(s)

Not applicable because C3991003 is a Phase 1 study with no estimands on PK parameters

2.2.3. Additional Estimand(s)

Not applicable because C3991003 is a Phase 1 study with no estimands on exploratory or tertiary endpoints

2.3. Study Design

The purpose of this study is to evaluate the safety, tolerability, and PK of multiple doses of PF-07081532 in participants with T2DM, inadequately controlled on metformin. The study may also enroll non-diabetic participants with obesity.

The study will also assess the effect on PD biomarkers, including MDG.

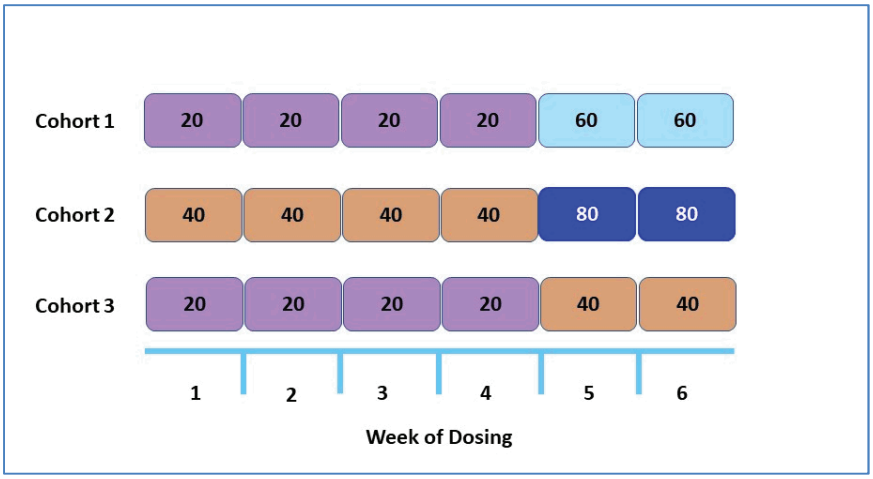
This is a randomized, double-blind (investigator- and participant- blind), sponsor-open, placebo-controlled, multiple oral dose-escalating study of PF-07081532.

In this study, adult participants with T2DM inadequately controlled on metformin will be enrolled and will receive PF-07081532 or placebo daily, for 42 days.

- *Enrollment in 3 cohorts is planned with approximately 12 participants (9 PF-07081532: 3 placebo) per cohort.*

A sample dosing scheme is provided below. Dosing in Cohort 1 will be conducted as shown. Increments in doses and duration of dosing at each step for subsequent cohorts, as well as the number of cohorts conducted, may be adjusted based on emerging data. The dosing scheme for each cohort will be provided in writing prior to its initiation.

Figure 1. Dose Titration Scheme



If a participant does not tolerate dose increment to the next dose level, as determined by the investigator and with notification to the sponsor, the participant may be reverted to the previously tolerated dose level. Following this dose modification, 2 separate attempts at increasing the dose to the next dose level are permitted, per investigator discretion. If, per investigator assessment, unacceptable intolerance (eg, severe vomiting) occurs shortly following dose administration, the dose will not be re-administered on the same day, and the participant may resume dosing at the current dose level at the next scheduled dosing time. Participants whose dose level is tolerability-limited may continue in the study for the intended duration of their assigned cohort at their own individual MTD, as judged to be appropriate by the PI and sponsor.

The planned cohorts in the study (Cohorts 1-3) may be conducted concurrently, partially overlapping or sequentially. The sponsor may decide not to conduct all planned cohorts, if it is judged that study objectives have been met. Up to 3 additional cohorts may be enrolled if judged necessary to meet the study objectives. One or more of the study cohorts may be conducted in non-diabetic participants with obesity.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Baseline is defined as the assessments performed on Day -1 for all endpoints, unless otherwise specified.

3.1. Primary Endpoint(s)

The safety endpoints which will be measured during the study constitute the primary endpoints. Where applicable, details of the endpoints to be derived and definition of baseline are also provided.

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;*
- *ECG results.*

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 or on 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 IP.

Adverse events occurring up to the first dose of active treatment on Day 1 will be considered non-treatment emergent.

A 3-tier approach for summarizing AEs will not be used for this study as there is a low number of subjects planned to be enrolled per treatment group, although risk differences and related summaries for AEs of interest will be presented as defined in 3.4.1.1.

3.1.1.1. Hypoglycemia Monitoring and Reporting

Hypoglycemia AEs will be recorded in the AE Case Report Form (CRF) with details of the event captured on the Hypoglycemic Event Details CRF. Details of when these will be recorded are given in the protocol (Section 8.2.4.2).

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 PI based on the protocol definition.
- Documented Symptomatic Hypoglycemia: If (2 – Did the participant have symptoms of hypoglycemia?) Yes and (3 – Was the blood glucose measured?) Yes and result

<70 mg/dL (or <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 (or <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. Safety Laboratory Tests

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

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 result assessed on Day -1.

3.1.3. Vital Signs

Vital sign measurements (systolic blood pressure, diastolic 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 collected at each appropriate assessment time will be calculated for each vital sign parameter.

Baseline will be defined as the result assessed on Day -1 per SoA, where "result" refers to the average of a triplicate measurement.

Changes from baseline for supine systolic and diastolic blood pressure and pulse rate will be calculated for each post baseline measurement.

The time-matched double difference in supine blood pressures and pulse rate measurements is calculated in the following steps: (1) subtract the average of the triplicate predose values 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. Electrocardiograms

Standard 12-lead ECG (including heart rate, QT, QTcF, PR and QRS interval) 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.

ECG endpoints include heart rate, QT interval, PR interval and QRS interval. If not supplied QTcF will be derived using Fridericia's heart rate correction formula:
QTcF = QT / (RR)^(1/3), where RR = 60/HR (if RR is not provided).

Baseline will be defined as the result assessed on Day -1 per SoA, where "result" refers to the average of a triplicate measurement.

Change from baseline for heart rate, QT, QTcF, PR and QRS interval will be calculated for each post baseline measurement.

The time-matched double difference in heart rate, QT, QTcF, PR and QRS measures is calculated in the following steps: (1) subtract the average of the triplicate predose values 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)

3.2. Secondary Endpoint(s)

Blood samples for PK analysis of PF-07081532 will be taken according to the Schedule of Activities given in the protocol.

Plasma PF-07081532 PK parameters following single or multiple dose administration of PF-07081532 will be derived using standard noncompartmental methods, as data permit, for each treatment and day (as appropriate), from the concentration time profiles as follows:

Table 2. PF-07081532 PK Parameters

Parameter	Analysis Scale	PF-07081532	Assessment Day
AUC_{24}	Ln	D	D1 and D42
AUC_{24}(dn)	Ln	D	D1 and D42
C_{max}	Ln	D	D1 and D42
C_{max}(dn)	Ln	D	D1 and D42
T_{max}	R	D	D1 and D42
$t_{1/2}$*	R	D	D42
PTR	Ln	D	D42
R_{ac}	Ln	D	D42
C_{av}	Ln	D	D42
C_{min}	Ln	D	D42
$R_{ac,Cmax}$	Ln	D	D42
CL/F*	Ln	D	D42
V_Z/F*	Ln	D	D42
AUC_{inf}*	Ln	D	D42
AUC_{last}	Ln	D	D42

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

3.3. Other Endpoint(s)

3.3.1. Change from Baseline in Insulin, Glucagon and C-Peptide AUC_{0-4}

Baseline for Insulin, Glucagon and C-Peptide AUC_{0-4} following MMTT will be defined as the AUC_{0-4} assessed on Day -1.

Change from baseline, percent change from baseline and relative change from baseline at the end of the study (ie Day 42 for Insulin, Glucagon and C-Peptide AUC_{0-4}) as specified in the schedule of activities will be calculated.

Note: Relative Change from Baseline = Post-dose timepoint Value / Baseline Value

3.3.2. Change from Baseline in Fasting Plasma Glucose, Fasting Plasma Insulin and HOMA-IR

The change from baseline to all post-dose timepoints as specified in the schedule of activities will be calculated.

Remark: Where triplicate fasting plasma insulin (FPI) are assessed, the average of the three measurements will be calculated to be reported at each timepoint and used to derive HOMA-IR. *When three assessements are performed at baseline, FPI baseline will be the average of the three values.*

3.3.3. Change from Baseline in HbA1c

Baseline for HbA1c will be defined as the Day -1. The change from baseline to all post-dose timepoints as specified in the schedule of activities will be calculated.

3.3.4. Change from Baseline in TSH

Baseline for TSH will be defined as the Day -1, 0H time point. The change from baseline to all post-dose timepoints as specified in the schedule of activities will be calculated.

3.3.5. Change from Baseline in FreeT4, Calcitonin, Amylase, Lipase, and Lipids

Baseline for freeT4, calcitonin, amylase, lipase, and lipids will be defined as the Day -1, 0H time point. The change from baseline to all post-dose timepoints as specified in the schedule of activities will be calculated.

3.3.6. Change from Baseline in Body Weight

Baseline for body weight will be defined as the pre-dose measure on Day 1. The change from baseline and percent change from baseline to all post-dose timepoints as specified in the schedule of activities will be calculated.

3.3.7. Baseline Variables

Baseline measures will be included as a covariate in all applicable statistical.

3.4. Other Safety Endpoints

3.4.1.1. Adverse events of interest

The TEAEs of interest for additional reporting are: nausea, vomiting and diarrhoea (as defined based on preferred term). Based on emerging blinded data reviews, other AEs of interest may be added to this list, which would be documented with a SAP amendment or documented in the changes to planned analysis section in the CSR.

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, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. 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. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.*

Participant Analysis Set	*Description*
Full Analysis Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.*
Safety Analysis Set	*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 Set	*The PK concentration population is defined as all randomized participants who received at least 1 dose of PF-07081532 and in whom at least 1 plasma concentration value is reported.*
PK Parameter Set	*The PK parameter population is defined as all randomized participants that received at least 1 dose of PF-07081532 and have at least 1 of the PK parameters of interest calculated.*
PD population Set	*The PD population set is defined as all randomized participants that received at least 1 dose of PF-07081532 and have at least 1 of the PD parameters of interest calculated.*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Not applicable

5.2. General Methods

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. Longitudinal Analysis using Mixed Model Repeated Measures (MMRM) model

MMRM models will include the change from baseline of the relevant endpoints as specified in Section 6 as the dependent variable and will include treatment, baseline, day, baseline*day interaction and the day*treatment interaction, with day fitted as a repeated effect, and participant as a random effect.

An unstructured covariance matrix will be used to estimate the variances and covariance within participant across time points. If convergence is not obtained or model fit is not adequate then other covariance structures (eg CS) will be investigated as necessary. The

Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. Missing values will be imputed as part of the MMRM model assumptions.

The Least Squares Means (LSMeans) together with 90% confidence intervals and standard errors will be obtained for each treatment and day. Differences in LSMeans between each treatment and placebo, together with 90% confidence intervals and standard errors, will also be obtained.

Standard SAS output will be provided to support the main statistical summary table for the models.

5.2.4. Analysis of Covariance (Raw Scale)

The ANCOVA model will include the change from baseline of the relevant endpoint as specified in Section 6 as the dependent variable and will include treatment as a fixed effect and baseline as a covariate.

Missing values will not be imputed.

The Least Squares Means (LSMeans) together with 90% confidence intervals and standard errors will be obtained for each treatment. Differences in LSMeans between each treatment and placebo, together with 90% confidence intervals and standard errors, will also be obtained.

Standard SAS output will be provided to support the main statistical summary table for the models.

Example SAS code is provided in the Appendices.

5.2.5. Analysis of Covariance (Log Scale)

The ANCOVA model will include the natural logarithmic transformed of relative change from baseline of the relevant endpoint as specified in Section 6 as the dependent variable and will include treatment as a fixed effect and log(baseline) as a covariate.

Missing values will not be imputed.

The adjusted geometric Least Squares Means (LSMeans) together with 90% confidence intervals and standard errors will be obtained for each treatment. Differences in adjusted geometric LSMeans between each treatment and placebo, together with 90% confidence intervals and standard errors, will also be obtained.

Standard SAS output will be provided to support the main statistical summary table for the models.

Example SAS code is provided in the Appendices.

5.2.6. Cumulative Incidence Plots

Cumulative Incidence Plots 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 group separately and will be plotted on the same graph. This will be based on plotting the cumulative incidence function (with no competing risks), which will be presented as a % on the y-axis. No statistical testing for differences between treatment groups will be considered.

Details of censoring are included in Section 6.2.1.2 and example SAS code is provided in the Appendices.

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. Pharmacokinetic 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/clinical team.

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 dose with ≥3 evaluable measurements.

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

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

5.3.4. 4-β-hydroxycholesterol/cholesterol ratio

Rules described in Section 5.3 will be used to manage concentrations below limit of quantification, deviations, missing concentrations and anomalous values.

5.3.5. Pharmacodynamic Parameters

For baseline AUC_{0-4} calculations, if participants have a missing baseline (ie, Day -1) 0 hour value, no imputation will be made. No imputation will be made for other missing values.

AUC_{0-4} will only be calculated in any participant with at least the first, last, and 75% of the total number of samples within the given interval available. Nominal times will be used in the calculation. No imputation for missing values will be conducted for these PD endpoints.

If the concentrations are below the limits of quantification such values will be truncated at the limit of quantification for all summaries and analyses, and will appear as reported in all listings.

The same principles apply to the analyses of all other PD endpoints.

6. ANALYSES AND SUMMARIES

Data collected before baseline will only be listed , unless otherwise stated.

In case of additional cohorts with non-diabetic participants with obesity, for all relevant analyses, the placebo arm will be presented as two separate treatment groups for the T2DM participants and non-diabetic participants with obesity.

6.1. Baseline Variables

Not applicable

6.2. Primary Endpoint

6.2.1. Safety Analysis

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

A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-07081532.

No formal analyses are planned for safety data. The safety and other endpoints detailed in Section 3.1 will be listed and summarized in accordance with sponsor reporting standards, Disposition of Subjects

Subject evaluation groups will show end of study subject disposition. Frequency counts will be supplied for subject discontinuation(s) by treatment.

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

6.2.1.1. Demographic and Physical Examination Data

A breakdown of demographic data will be provided for age, gender, race, and ethnicity (T2DM and non-diabetic obesity, summarized separately). The physical measurement - height; weight; body mass index; duration of T2DM (for T2DM participants only) - at baseline will also be summarized. Each will be summarized by treatment and 'All Subjects' in accordance with the sponsor reporting standards.

An additional table listing the screening data of free T4, TSH, calcitonin, amylase, lipase, C-peptide and HbA1c will be produced as above.

6.2.1.2. Discontinuation(s)

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

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

6.2.1.3. 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 and overall.

A set of individual profile plots will be produced separately for each TEAE of interest. Each plot will include horizontal bars by participant which will represent if/when a participant experienced the TEAE of interest (measured in days). The x-axis will represent time and the bars will be colored by severity, with the plots paged by treatment group. Multiple events for the same participant of the same TEAE would therefore be represented by multiple horizontal bars.

Time to the first occurrence of TEAEs of interest will be produced using Cumulative Incidence Plots as described in Section 5.2.6. Participants who discontinue from the study, discontinue from IP will be censored at the discontinuation/initiation date.

A separate plot for each TEAE will be produced separately.

The above will also be produced separately for the time to the first recurrence of the TEAEs of interest. There will be a separate line for each treatment group.

6.2.1.4. Hypoglycemia

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

6.2.1.5. 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.

6.2.1.6. Vital Signs Data

Average of the triplicate measurements (where applicable) will be used in analyses.

Unless specified otherwise, for non-maximum summaries unplanned assessments will not be considered.

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by treatment group and time point, according to sponsor reporting standards. Tables will be paged by parameter.

Baseline is as defined in Section 3 .

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 group with all treatments on the same plot.

For baseline subtracted supine systolic and diastolic blood pressure and pulse rate, the differences between each treatment group of PF-07081532and placebo (treatment – placebo, using the placebo from the respective population) will be summarized (N, mean, 90% CI) and plotted (mean, 90% CI) for each treatment group of PF-07081532and time point.

Participants with absolute values and changes from baseline for vital signs (over all post-dose measurements) meeting categories as defined in the Appendix 2 will also be summarized descriptively by treatment group. 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.

Maximum decrease and increase from baseline for supine systolic and diastolic blood pressures, and maximum increase from baseline for supine pulse rate will be summarized by treatment group, according to sponsor reporting standards.

Data from all cohorts will be plotted on the same figure using a single line for the placebo group(s). Corresponding individual plots of change from time-matched baseline will also be produced for each treatment.

The time-matched double differences in vital signs obtained following the Day 1 treatment, as defined in Section 3 , will be summarized (N, mean, 90% confidence interval) for each treatment and time point. In addition, the time-matched double differences between each treatment and placebo will be summarized (N, mean, 90% confidence interval) for each treatment, time post-dose and day.

Mean time-matched double differences in vital signs will be plotted against time post-dose for each Day as defined in the SoA 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 mean plots will similarly be produced for the time-matched double differences between each treatment and placebo.

6.2.1.7. Electrocardiograms Data

Average of the triplicate measurements (where applicable) will be used in analyses.

Unless specified otherwise, for non-maximum summaries unplanned assessments will not be considered.

Absolute values and changes from baseline in QT interval, heart rate, QTcF interval, PR and QRS will be summarized by treatment group and time point using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3 .

Mean changes from baseline in QT interval, heart rate and QTcF will be plotted against time point. On each plot there will be 1 line for each treatment group with all treatments included on the same plot.

In addition for baseline subtracted QT, heart rate and QTcF, the differences between each treatment group of PF-07081532 and placebo (treatment – placebo, using the placebo from the respective population) will be summarized (N, mean, 90% CI) and plotted (mean, 90% CI) for each treatment group of PF-07081532 and time point.

Participants with ECG endpoints and changes from baseline (QTcF, PR and QRS) meeting categories as defined in the Appendix 2 (for QTcF these correspond to the Pfizer Guidance [2]) will also be summarized descriptively by treatment group. 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.

Maximum absolute value (post-dose) and the maximum increase from baseline for QTcF, PR and QRS will be summarized by treatment group according to sponsor reporting standards.

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

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

The time-matched double differences in QT, QTcF, PR, QRS intervals and heart rate measures obtained following the Day 1 treatment, as defined in Section 3.1, will be summarized (N, mean, 90% confidence interval) for each treatment and time point. In addition, the differences between each treatment and placebo will be summarized (N, mean, 90% confidence interval) for each treatment, time postdose and day.

Mean time-matched double differences in ECG parameters will be plotted against time postdose for each Days as defined in the SoA 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 mean plots will similarly be produced for the time-matched double differences between each treatment and placebo.

The time-matched double differences in QTcF will be plotted against PF-07081532 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.

6.3. Secondary Endpoint(s)

6.3.1. PF-07081532 PK Parameters

- Estimand strategy: Not applicable

- Analysis set: PF-07081532 Concentration and Pharmacokinetic Parameter Set

To assess the pharmacokinetics of PF-07081532, the PK parameters detailed in Section 3.2 will be listed and summarized for participants in the PK analysis set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3 along with handling of values where participants received a dose that was not assigned based on the titration scheme). Each PK parameter will be summarized by treatment (eg differentiating different doses and dosing frequencies as required), and Study Day (Day 1, and 42, as applicable).

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

Table 3. PF-07081532 PK Parameters to be Summarized Descriptively

Parameter	Matrix	Summary Statistics
AUC_{24}, AUC_{24}(dn), C_{max}, C_{max}(dn), PTR, R_{ac}, C_{av}, C_{min}, $R_{ac,Cmax,,}$, CL/F, Vz/F, $AUC_{inf,}$ AUC_{last}	Plasma	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	Plasma	N, median, minimum, maximum.

$t_{1/2}$	Plasma	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

There will be one summary table presenting all PK parameters. The treatment subheading will include the analyte, matrix, dose information and day (Day 1, or Day 42). As per Section 5.3.3, data collected on days that participants received anything other than the assigned dose based on the titration scheme will only be listed and not summarized as part of the summary table.

To assess the relationship between the PK parameters and dose for PF-07081532, dose normalized AUC_{24} and C_{max} will be plotted against treatment (using a logarithmic scale) for Day 1, and Day 42 separately and will include individual participant values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented.

The observed accumulation ratio for AUC_{24} and C_{max} will be analyzed after natural log transformation using a one-way analysis of variance with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation for each dose.

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.

Presentations for PF-07081532 concentrations will include:

- a listing of all concentrations sorted by participant ID, treatment, day and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

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

- median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose), for Day 1 and Day 42 .

- mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose), for Day 1 and Day 42.

- individual concentration time plots by treatment (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each treatment per scale), paged by day (and also equivalent plots spanning the entire study duration – not paged by day).

- Median trough concentrations time plots (on both linear and semi-log scales) against nominal time post dose by treatment, spanning the entire study duration, i.e. not paged by day (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose)

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-07081532 concentration is quantifiable in the matrix.

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

6.4. Other Endpoint(s)

6.4.1. Change from Baseline in Insulin, Glucagon and C-Peptide AUC_{0-4}

- Estimand strategy: Not applicable

- Analysis set: Pharmacodynamic Population Set

- The natural log-transformed of the relative change from baseline at the end of the study will be included in an ANCOVA model, as described in Section 5.2.5, for each measure separately. The adjusted geometric LSMeans and adjusted geometric LSMean differences to placebo (with 90% confidence intervals) will be calculated and plotted.

Absolute values and percent change from baseline will be summarized descriptively by treatment and day as described in Section 5.2.1.

6.4.2. Change from Baseline in Fasting Plasma Glucose, Fasting Plasma Insulin and HOMA-IR

- Estimand strategy: Not applicable

- Analysis set: Pharmacodynamic Population Set

Absolute values and change from baseline will be summarized descriptively by treatment and timepoint (when applicable) as described in Section 5.2.1.

The change from baseline over time for FPG will be included in an MMRM model as described in Section 5.2.3. The LSMeans and LSMean differences to placebo (with 90% confidence intervals) will also be plotted.

The change from baseline over time for FPI and HOMA-IR will be included in an ANCOVA model, as described in Section 5.2.4, for each measure separately. The LSMeans and LSMean differences to placebo (with 90% confidence intervals) will also be plotted.

6.4.3. Change from Baseline in HbA1c

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

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

The change from baseline over time will be included in an MMRM model as described in Section 5.2.3. The LSMeans and LSMean differences to placebo for each timepoint (with 90% confidence intervals) will be plotted.

6.4.4. 4-β-hydroxycholesterol/Cholesterol Ratio

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

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

Absolute values, and percent change from baseline will be summarized descriptively by treatment and day as per Section 5.2.1.

The percent change from baseline over time will be analyzed with an ANCOVA model as described in Section 5.2.5. The LSMeans and LSMean differences to placebo (with 90% confidence intervals) will be plotted. Results of this analysis may be not included in the CSR.

6.5. Subset Analyses

Not applicable

6.6. Baseline and Other Summaries and Analyses

Where relevant, data will be reported in accordance with the sponsor reporting standards.

6.6.1. Baseline Summaries

A baseline table (or separate tables, as required) summarizing the following will be produced by treatment group and overall (T2DM and non-diabetic obesity, summarized separately): HbA1c; fasting plasma glucose; systolic blood pressure; diastolic blood pressure; pulse rate; and metformin total daily dose (for T2DM participants only).

6.6.2. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition for each phase of the study (screening, double-blind treatment and follow-up) and will additionally show which participants were analyzed for safety, for PK and for tertiary endpoints. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment group and overall.

CCI [redacted]

6.6.4. Concomitant Medications and Nondrug Treatments

All prior and concomitant medication(s) as well as non-drug treatment(s) will be reported according to current sponsor reporting standards.

6.6.5. Discontinuations

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

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

6.7. Safety Summaries and Analyses

Not applicable

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. As this is a 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 dose selection decisions, facilitating PK/PD modeling, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

3. ICH Harmonised Guideline E9 (R1); Estimands and Sensitivity Analysis in Clinical Trials; 16 June 2017.

4. Pfizer Guidance for Evaluation of QT / QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs; Members of the Cardiovascular Safety & Advisory Council (CVSAC); January 26, 2018.

APPENDICES

Appendix 1. Statistical Methodology Details

Example SAS code for MMRM Model:

```
proc mixed data = dataset method=reml;
        class subject treatment time;
        model cfb = treatment base time base*time time*treatment / ddfm=kr residual
outp=resid_out;
        repeated time /subject=subjid type = un;
        lsmeans treatment*time/diff cl alpha=0.1;
        ods output lsmeans=lsmeans_out;
        ods output diffs=diffs_out;
run;
```

Example SAS code for Cumulative Incidence Plots:

```
proc lifetest data = dataset method=km plots=cif(test) outcif=cifatrisk intervals=0 to 20 by 2;
        strata treatment;
        time day*censor(1)/eventcode=0;
run;
```

NOTE: the censor variable has a value = 1 when the related time is censored and has a value = 0 when the event of interest occurs. There should be no other values available for this censored variable in this dataset (including missing values). If required, missing observations should be removed prior to analysis.

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

Appendix 3. List of Abbreviations

Abbreviation	Term
Abs	Absolute
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
BA	Bioavailability
BE	Bioequivalence
BLQ	below the limit of quantitation
BOCF	baseline observation carried forward
BP	blood pressure
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CI	confidence interval
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
EAC	event adjudication committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
FAS	full analysis set
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GLIMMIX	generalized linear mixed-effects model with repeated measures
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
ICH	International Council for Harmonisation
IRC	internal review committee
IST	independent statistical team
ITT	intent-to-treat
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MAR	missing at random

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures
MNAR	missing not at random
N/A	not applicable
NNB	number needed to benefit
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
PPAS	per-protocol analysis set
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RCDC	reverse cumulative distribution curve
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGS	Statistical Guidance Standards
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TA	therapeutic area
ULN	upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary