**Protocol C3421008**

# A 12-WEEK, PHASE 2A, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACODYNAMICS OF PF-06882961 TITRATION IN ADULTS WITH TYPE 2 DIABETES MELLITUS TREATED WITH METFORMIN AND IN NON-DIABETIC ADULTS WITH OBESITY

**Statistical Analysis Plan**
**(SAP)**

**Version:** 2.0

**Date:** 29 Nov 2021

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

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## APPENDICES

## 1. VERSION HISTORY

**Table 1. Summary of Changes**

| Version/ Date | Associated Protocol Amendment | Rationale | Specific Changes |
|---|---|---|---|
| 1.0<br>30th Nov 2020 | Amendment 2 (23 Sep 2020) | Original protocol was amended twice prior to first subject first visit | N/A |
| 2.0<br>29th Nov 2021 | Amendment 2 (23 Sep 2020) | Updates based on SAP template update, Blinded Data Reviews and requirement for certain sites to derive QTcF manually and enter into CRF. | Minor updates to page header and footers, section numbering and list of abbreviations. *Rationale:* update to latest SAP template.<br><br>Sections 3.5.3.1 & 6.5.1: added parameters to list of endpoints. *Rationale:* needed for reporting.<br><br>Section 3.5.5: included formula to derive QTcF for reporting. *Rationale:* to ensure QTcF calculation is consistent across sites.<br><br>Sections 3.5.6, 6.6.5 & Appendix 6: included details on mental health assessment definitions and analyses. *Rationale*: erroneously missed endpoints in version 1 of SAP.<br><br>Sections 3.5.3.2, 6.1.1.2.4, 6.1.1.2.5, 6.2.1.1, 6.3.1, 6.6.3 & 6.6.4: minor updates to definitions or inclusion of more details. *Rationale:* clarification.<br><br>Sections 6.1.1.2.4, 6.1.1.2.5.1, 6.1.1.2.8, 6.1.1.2.10, 6.5.4, 6.5.5, 6.6.2, 6.6.2.2, 6.6.3 & 6.6.4: |

| | | | |
|---|---|---|---|
| | | | additional overall summarization included. *Rationale:* to provide an overview of the study population.<br><br>Section 6.6.2.1: added %change from baseline MMRM analyses for a subset of safety lab parameters. *Rationale*: permit a more comprehensive review of additional safety lab parameters.<br><br>Section 6.6.4: removed summaries of differences to placebo for ECG parameters. *Rationale*: MMRM analyses already included provide a more comprehensive assessment of these safety parameters.<br><br>Section 6.5.2: added summary table of important protocol deviations. *Rationale*: standard table required for CSR reporting. |

## 2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3421008. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

### 2.1. Study Objectives, Endpoints, and Estimands

| ***Objectives*** | ***Endpoints*** | ***Estimands*** |
|---|---|---|
| ***Primary:*** | ***Primary:*** | ***Primary:*** |
| • *To evaluate the tolerability of different titration schemes of PF-06882961 administered for 12 weeks to participants with T2DM and the tolerability of a single titration scheme in non-diabetic participants with obesity.* | • *Incidence and severity of treatment emergent AEs.* | • *There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.* |
| ***Secondary:*** | ***Secondary:*** | ***Secondary:*** |
| • *To evaluate the safety of different titration schemes of PF-06882961 administered for 12 weeks to participants with T2DM and the safety of a single titration scheme in non-diabetic participants with obesity.* | • *Incidence of clinical laboratory abnormalities, vital signs (blood pressure and pulse rate) and ECG parameters (heart rate, QT, QTcF, PR and QRS intervals).*<br>• *Assessment of mental health as determined by C-SSRS and PHQ-9.* | • *There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.* |
| • *To evaluate the effect on fasting plasma glucose of different titration schemes of PF-06882961 administered for 12 weeks to participants with T2DM.* | • *Change from baseline in fasting plasma glucose at Weeks 2, 4, 6, 8, 10 and 12.* | • *Estimand 1A: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in participants with T2DM on stable doses of metformin without the benefit of glycemic rescue medication while on treatment.* |
| • *To evaluate the effect on HbA1c of different titration schemes of PF-06882961 administered for 12 weeks to participants with T2DM.* | • *Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 10 and 12.* | • *Estimand 2A: This estimand will be the same as 1A.* |
| • *To evaluate the effect on body weight of different titration schemes of PF-06882961 administered for 12 weeks to participants with T2DM.* | • *Change from baseline in body weight at Weeks 2, 4, 6 8, 10 and 12.* | • *Estimand 3A: This estimand will be the same as 1A.* |

| ***Objectives*** | ***Endpoints*** | ***Estimands*** |
|---|---|---|
| • *To evaluate the effect on body weight of a single titration scheme of PF-06882961 administered for 12 weeks to non-diabetic participants with obesity.* | • *Change from baseline in body weight at Weeks 2, 4, 6 8, 10 and 12.* | • *Estimand 3B: This estimand will be the same as 1B.* |
| ***Tertiary/Exploratory:*** | ***Tertiary/Exploratory:*** | ***Tertiary/Exploratory:*** |
| • *To evaluate the effect on fasting plasma glucose of a single titration scheme of PF-06882961 administered for 12 weeks to non-diabetic participants with obesity.* | • *Change from baseline in fasting plasma glucose at Weeks 2, 4, 6, 8, 10 and 12.* | • *Estimand 1B: This estimand is intended to provide a population level estimate of the mean treatment effect (PF-06882961 versus placebo) on a continuous endpoint in non-diabetic obese participants with obesity while on treatment.* |
| • *To evaluate the effect on HbA1c of a single titration scheme of PF-06882961 administered for 12 weeks to non-diabetic participants with obesity.* | • *Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 10 and 12.* | • *Estimand 2B: This estimand will be the same as 1B.* |
| • *To summarize the pharmacokinetics of PF-06882961 in participants with T2DM and in non-diabetic participants with obesity.* | • *Pre-dose plasma concentration of PF-06882961 on Days, 14, 28, 42, 56, 70, 84 and at 2-6 hours post-dose on Days 1, 42, 84.* | • *There are no defined estimands for these endpoints and they will be analyzed using Pfizer data standards as applicable.* |
| • *To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.* | • *Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).* | |

### 2.1.1. Primary Estimand(s)

N/A

### 2.1.2. Secondary Estimand(s)

*Estimand 1A will be the population average treatment effect on the change from baseline in* fasting plasma glucose (FPG) *of PF-06882961 compared to placebo in participants with T2DM in the absence of glycemic rescue medication while on treatment and stable doses of background metformin. This reflects a combination of the 'Hypothetical' and 'While on treatment' strategies as outlined in the ICH-E9 (R1) draft guidance.*[1]

*Measurements after initiation of glycemic rescue medication or discontinuation of IP will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a missing at random (MAR) assumption. Participants with inadequate compliance will have their fasting plasma glucose values used as-is in the analysis. The population-based treatment effect will be the difference in the mean change from baseline in each PF-06882961 arm compared to placebo. This estimand will be applied to the changes from baseline in FPG at Weeks 2, 4, 6, 8, 10 and 12.*

*Estimands related to other endpoints:*

*Estimands 2A and 3A will utilize the same approach as Estimand 1A for the associated endpoints.* Similarly, Estimand 3B will utilize the same approach as Estimand 1B (described in Section 2.1.3) for the associated endpoint.

The above estimands related to T2DM participants on a background of metformin (1A, 2A and 3A) include the following 4 attributes:

- Population: Defined by the inclusion and exclusion criteria to reflect participants with T2DM who are on a background of metformin
- Variable: Change from baseline at Weeks 2, 4, 6, 8, 10 and 12 for FPG, HbA1c and Body Weight for Estimands 1A, 2A and 3A, respectively
- Intercurrent events: Measurements after initiation of glycemic rescue medication and/or discontinuation of study investigational product (IP) will be censored
- Population-level summary: Difference of variable means between PF-06882961 (each treatment group considered separately) and placebo

### 2.1.3. Additional Estimand(s)

*Estimand 1B will be the population average treatment effect on the change from baseline in FPG of PF-06882961 compared to placebo in non-diabetic participants with obesity, while on treatment. This reflects a combination of the 'Hypothetical' and 'While on treatment' strategies as outlined in the ICH-E9 (R1) draft guidance.*[1]

*Measurements after discontinuation of IP will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a missing at random (MAR) assumption. Participants with inadequate compliance will have their fasting plasma glucose values used as-is in the analysis. The population-based treatment effect will be the difference in the mean change from baseline in each PF-06882961 arm compared to placebo. This estimand will be applied to the changes from baseline in FPG at Weeks 2, 4, 6, 8, 10 and 12.*

*Estimands related to other endpoints:*

Estimand 2B will utilize the same approach as Estimand 1B for the associated endpoints.

These above estimands related to non-diabetic participants with obesity (1B, 2B and 3B) include the following 4 attributes:

- Population: Defined by the inclusion and exclusion criteria to reflect non-diabetic participants with obesity
- Variable: Change from baseline at Weeks 2, 4, 6, 8, 10 and 12 for FPG, HbA1c and Body Weight for Estimands 1B, 2B and 3B, respectively
- Intercurrent events: Measurements after discontinuation of study IP will be censored
- Population-level summary: Difference of variable means between PF-06882961 (each treatment group considered separately) and placebo

### 2.2. Study Design

*This Phase 2a, multicenter, randomized, double-blind, sponsor-open, placebo-controlled, parallel-group, study will assess tolerability, safety, and pharmacodynamics (PD) of BID administration of PF-06882961 in adult participants with T2DM who are treated with metformin. In addition, participants with obesity, without T2DM, will be enrolled to explore differences in tolerability, safety, pharmacokinetics and pharmacodynamics between participants with T2DM and participants without T2DM and to support clinical development in both T2DM and obesity.*

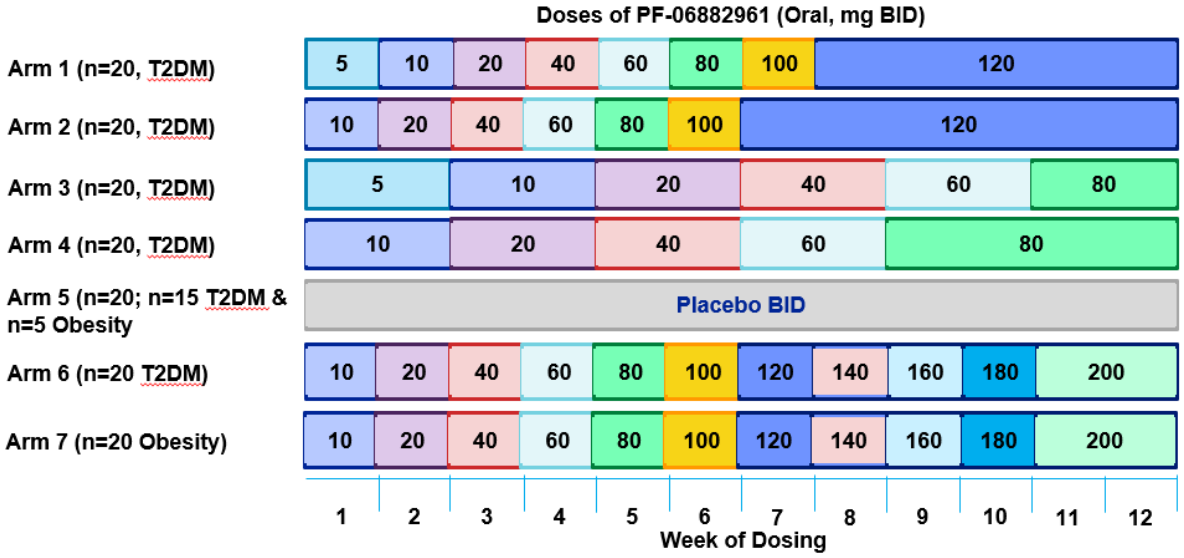
*For participants with T2DM, the metformin dose (at least 500 mg/day) must have been stable for at least 60 days prior to the screening visit (Visit 1) and should remain the same until the first follow-up visit (ie, Visit 10, Week 13-14), except in circumstances where a dose change is deemed medically necessary.*

*Following the screening period to confirm eligibility (up to 4 weeks), the study will consist of a 2-week single-blind placebo run-in period, prior to randomization on Day 1. Following randomization, participants with T2DM will be assigned to either the placebo arm or 1 of the 5 active treatment arms with PF-06882961. PF-06882961 doses will be titrated to a target dose of 80 mg BID in 2 arms, 120 mg BID in 2 arms, and 200 mg BID in 1 arm.*

*Following randomization, participants with obesity will be assigned to either the placebo arm or an active treatment arm with PF-06882961 with a target dose of 200 mg BID.*

*The treatment period will be 12 weeks, followed by an approximate 4-week follow-up. The total duration of participation in this study is approximately 18 weeks, not including the screening period. Dosing with PF-06882961 or placebo will occur BID with food in the morning and evening. Refer to* **Figure 1** *for details of dose titration schemes per study arm, in which the doses depicted in Arms 1 to 7 are administered BID.*

**Figure 1. Dose Titration Scheme**




*Assuming a 25% drop-out rate, approximately 140 participants will be randomly assigned to IP such that approximately 105 evaluable participants complete the study. Of these approximately 140 randomized participants, approximately 115 participants will have T2DM and approximately 25 will have obesity without T2DM. For participants with T2DM, approximately 20 participants will be allocated to each of the 5 active arms and approximately 15 participants to the placebo arm. For participants with obesity without T2DM, approximately 20 participants will be allocated to Arm 7 and approximately 5 participants to the placebo arm. To ensure balance between the groups, randomization will be stratified based on biological sex (men vs. women). There are no plans to replace withdrawn participants.*

## 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

*Baseline is defined as the result closest prior to dosing at Visit 3 (Day 1)* for all endpoints, unless otherwise specified.

### 3.1. Primary Endpoint(s)

The primary endpoint is the incidence and severity of treatment emergent AEs per treatment group in participants with T2DM or non-diabetic participants with obesity. Adverse events are defined as per Section 3.5.1.

### 3.2. Secondary Endpoint(s)

- Change from baseline in FPG at Weeks 2, 4, 6, 8, 10 and 12 in participants with T2DM.
- Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 10 and 12 in participants with T2DM.

- Change from baseline in body weight at Weeks 2, 4, 6, 8, 10 and 12 in participants with T2DM.

- Change from baseline in body weight at Weeks 2, 4, 6 8, 10 and 12 in non-diabetic participants with obesity.

For duplicate measurements of body weight, the average of the duplicate body weight readings collected at each assessment time will be calculated prior to summaries/analysis. If one of the two duplicates are missing, the non-missing value will be used, and missing values will not be imputed.

### 3.3. Other Endpoint(s)

- Pre-dose plasma concentration of PF-06882961 on Days, 14, 28, 42, 56, 70, 84 and at 2-6 hours post-dose on Days 1, 42 and 84 in participants with T2DM or non-diabetic participants with obesity.

- Change from baseline in FPG at Weeks 2, 4, 6, 8, 10 and 12 in non-diabetic participants with obesity.

- Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 10 and 12 in non-diabetic participants with obesity.

### 3.4. Baseline Variables

Baseline measures will be included as a covariate in all applicable statistical models along with the stratification variable of female versus male (see Section 4.1).

### 3.5. Safety Endpoints

#### 3.5.1. 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 during the placebo run-in period (i.e. from Day –14 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 Section 6.1.1.2.2.

#### 3.5.1.1. 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.

#### 3.5.1.2. Subset reporting interval

A subset reporting interval of the TEAEs of interest (as defined in Section 3.5.1.1) will be defined by a shorter reporting interval than that defined for the main reporting interval. This interval will include adverse events of interest (reported separately) if:

- the event starts after or on the first dose, but doesn't start more than two days after the last dose of IP (defined as either completing the 12 weeks of treatment or discontinuing from IP earlier).

CCI [redacted]

### 3.5.2. Hypoglycemic Monitoring

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.

### 3.5.3. Laboratory Data

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 closest prior to dosing at Visit 3 (Day 1).

#### 3.5.3.1. Change from 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)

- 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, total bilirubin, bile acids and gamma-glutamyl transferase [GGT]) to all post-dose time points as per the SOA

- Change from baseline in estimated glomerular filtration rate (eGFR) to all post-dose time points as per the SOA

### 3.5.3.2. Clinical Laboratory Parameters of Interest

For the specific laboratory parameters listed in the table below, the following endpoints will be derived:

- Abnormalities defined as either a "Flag Level" or "Alert Level" as in the table below

| Parameter | Flag Level | Alert Level | Conventional Units |
|---|---|---|---|
| Fasting Plasma Glucose | < 70<br>≥ 270 | ≤ 54<br>≥ 270 | mg/dL |
| Amylase | >ULN | Pfizer standard flag for PCC | U/L |
| Lipase | >ULN | Pfizer standard flag for PCC | U/L |
| Calcitonin | >ULN | Pfizer standard flag for PCC | pg/mL |
| Alanine Aminotransferase | ≥ 2 ULN | Pfizer standard flag for PCC | U/L |
| Aspartate Aminotransferase | ≥ 2 ULN | Pfizer standard flag for PCC | U/L |
| Alkaline Phosphatase | ≥ 2 ULN | Pfizer standard flag for PCC | U/L |
| Gamma Glutamyl Transferase | ≥ ULN | Pfizer standard flag for PCC | U/L |
| Total Bilirubin | > 1.5 ULN | Pfizer standard flag for PCC | mg/dL |
| Serum Total Bile Acids | >ULN | Pfizer standard flag for PCC | µmol/L |

PCC – potential clinical concern
ULN – upper limit of normal as determined by the central laboratory

These endpoints will be derived using both pre and post-dose data separately. Post-dose will include all post-baseline data including unplanned readings and pre-dose will include all data from the placebo run-in defined by including all values from Visit 2 to pre-dose, including the baseline measurement and unplanned readings. Note, both pre- and post-dose populations will be from the safety analysis set (defined in Section 4).

### 3.5.4. 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 closest prior to dosing at Visit 3 (Day 1), 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.

### 3.5.5. Electrocardiograms (ECGs)

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.

For reporting, QTcF will be derived based on the CRF entered heart rate and QT interval values as:

$$QTcF = \frac{QT\ Interval}{\sqrt[3]{\frac{60}{heart\ rate}}}$$

Where QT interval is in msec and heart rate is in beats/min. The CRF entered QTcF will therefore not be included in any analysis or reported in CSR tables.

Baseline will be defined as the result closest prior to dosing at Visit 3 (Day 1), 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.

### 3.5.6. Assessment of Mental Health

- Assessment of mental health as determined by Columbia-Suicide Severity Rating Scale (C-SSRS) and Patient Health Questionnaire-9 (PHQ-9).

The C-SSRS is a validated tool to evaluate suicidal ideation and behaviour. Data relevant to the assessment of suicidality will be mapped to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes as given in Appendix 6).

For this endpoint the screening visit will be labelled as 'Lifetime' in tables and the recent history (i.e. past 12 months) will also be reported separately.

*The PHQ-9 is a 9 item self-report scale for the assessment of depressive symptoms. The PHQ-9 will be completed by participants and reviewed by site staff at the pre-defined time points outlined in the* SOA.

The PHQ-9 total score will be derived for each time point separately by summing the responses to the 9 questions. Baseline is defined as the last pre-dose measurement.

## 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.

| Population | Description |
|---|---|
| *Enrolled* | *All participants who sign the ICD.* |
| *Randomly assigned to IP* | *All participants randomly assigned to IP regardless of whether or not IP was administered.* |
| *Evaluable* | *All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the randomized intervention.* |
| *Safety* | *All participants randomly assigned to IP and who take at least 1 dose of IP. Participants will be analyzed according to the product they actually received.* |

| ***Defined Population for Analysis*** | ***Description*** |
|---|---|
| *Estimand Set 1A (related to estimands 1A, 2A & 3A)* | *All evaluable participants with T2DM randomly assigned to IP and who take at least 1 dose of IP. For participants who discontinue IP and/or receive glycemic rescue medication, all subsequent values will be censored.* |
| *Estimand Set 1B (related to estimands 1B, 2B & 3B)* | *All evaluable non-diabetic participants with obesity randomly assigned to IP and who take at least 1 dose of IP. For participants who discontinue IP, all subsequent values will be censored.* |
| *PK Concentration Set* | *All participants randomly assigned to IP and who take at least 1 dose of PF-06882961 and in whom at least 1 concentration value is reported.* |

### 4.1. Strata Misallocations

Participants who are randomized to the wrong stratum, in error, will have the incorrect stratum assignment remain in IMPALA but the clinical database will include the correct stratum. The latter will subsequently be used for all relevant analyses.

## 5. GENERAL METHODOLOGY AND CONVENTIONS

### 5.1. Hypotheses and Decision Rules

Exploratory statistical analysis will be performed on the primary endpoint related to AEs of interest only (as defined in Section 3.5.1.1). For this analysis, the null hypothesis is that there

is no difference between treatment groups. The alternative hypothesis is that there is a difference between treatment groups. Note this will be applied to testing the difference between 2 separate treatment groups (rather than testing for differences across all treatment groups). The Type I error rate ($\alpha$-level) used for the statistical inference will be 5% (2-sided).

Statistical analysis will also be performed on the secondary endpoints related to Estimands: 1A and 1B related to change from baseline in FPG; 2A and 2B related to change from baseline in HbA1c; and 3A and 3B related to change from baseline in body weight. For these estimands, the null hypothesis is that there is no difference between PF-06882961 and placebo on the secondary endpoints. The alternative hypothesis is that PF-06882961 is superior (i.e. greater reduction) to placebo on the secondary endpoints. The Type I error rate ($\alpha$-level) used for the statistical inference will be 5% (1-sided). Each dose of PF-06882961 will be tested separately compared to placebo.

No adjustment for multiple comparisons will be made for any of the analyses described above, as the primary objective of this study is summarizing tolerability.

## 5.2. General Methods

The analyses related to the primary, secondary and exploratory endpoints will be based on the appropriate population for analysis (see Section 4).

Unless otherwise stated, all summaries and plots will be presented by treatment group. The following treatment group labels (or similar) will be used:

| Arm | Strata | Treatment group label |
|---|---|---|
| 5 | T2DM | Placebo (T2DM) |
| 5 | Non-diabetic obesity | Placebo (non-diabetic obesity) |
| 3 | T2DM | PF-06882961 80 mg BID low, slow (T2DM) |
| 4 | T2DM | PF-06882961 80 mg BID high, slow (T2DM) |
| 1 | T2DM | PF-06882961 120 mg BID low, fast (T2DM) |
| 2 | T2DM | PF-06882961 120 mg BID high, fast (T2DM) |
| 6 | T2DM | PF-06882961 200mg BID (T2DM) |
| 7 | Non-diabetic obesity | PF-06882961 200mg BID (non-diabetic obesity) |

### 5.2.1. Analyses for Continuous Endpoints

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

### 5.2.2. Analyses for Categorical Endpoints

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

### 5.2.3. Mixed Model Repeated Measures (MMRM)

The mixed model repeated measures (MMRM) *model will include treatment, time, strata (male versus female) and treatment-by-time interaction as fixed effects, baseline as a covariate and the baseline-by-time interaction with time fitted as a repeated effect and*

*participant as a random effect.* The baseline covariate will be based on the associated endpoint being analysed (i.e. for Estimands 1, 2 and 3, baseline FPG, HbA1c and body weight will be used, respectively).

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 will be investigated as necessary. The Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters.

Missing values (e.g. due to censoring) will be implicitly imputed as part of the MMRM model fitting.

The Least Squares Means (LSMeans) together with 90% confidence intervals, standard errors and p-values (2-sided) will be obtained for each treatment group at each time point.

Differences in LSMeans between each treatment group of PF-06882961 relative to placebo (from the same population) at each time point, together with 90% confidence intervals, standard errors and p-values (1-sided, unless otherwise stated), will also be obtained.

Example SAS code is provided in Appendix 2.

### 5.2.4. 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 Sections 6.5.6, 6.1.1.2.6 and 6.1.1.2.7 and example SAS code is provided in Appendix 2.

## 5.3. Methods to Manage Missing Data

For applicable continuous endpoints modelled with an MMRM, missing/censored values will be imputed as part of the analysis method.

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).

# 6. ANALYSES AND SUMMARIES

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

For all relevant analyses, treatment arm 5 (the placebo arm) will be presented as two separate treatment groups for the T2DM participants and non-diabetic participants with obesity.

## 6.1. Primary Endpoint(s)

### 6.1.1. Incidence and severity of treatment emergent AEs

#### 6.1.1.1. Main Analysis

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

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

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

#### 6.1.1.2. Sensitivity/Supplementary Analyses

The following exploratory safety analyses will be restricted to the TEAEs of interest (as defined in Section 3.5.1.1). All sets of outputs in this section would be produced separately for "all causality" TEAEs only.

##### 6.1.1.2.1. Forest plots on the Incidence of adverse events of interest

Forest plots displaying the incidence of TEAEs of interest ("All Causality" only) by treatment group will be produced separately by AE. Each forest plot will present all treatment groups separately (including the placebo groups) and will include 95% confidence intervals (calculated using the Blyth-Still-Casella method[2]).

##### 6.1.1.2.2. Risk differences for adverse events of interest

TEAEs of interest will be tabulated by treatment group, where the number of participants and percent will be presented, along with the risk difference between various treatment comparisons. These will be triaged according to the table below which aim to address different objectives as follows:

Triage Group 1: comparing treatment groups of PF-06882961 in T2DM
Triage Group 2: comparing treatment groups of PF-06882961 in T2DM versus non-diabetic obesity
Triage Group 3: comparing treatment groups for PF-06882961 versus placebo
Triage Group 4: other comparisons

| Triage Group | Comparisons |
|---|---|
| 1 | PF-06882961 120 mg BID high, fast (T2DM) vs. PF-06882961 120 mg BID low, fast (T2DM)<br>PF-06882961 80 mg BID high, slow (T2DM) vs. PF-06882961 80 mg BID low, slow (T2DM)<br>PF-06882961 120 mg BID low, fast (T2DM) vs. PF-06882961 80 mg BID low, slow (T2DM)<br>PF-06882961 120 mg BID high, fast (T2DM) vs. PF-06882961 80 mg BID high, slow (T2DM) |

| | |
|---|---|
| 2 | PF-06882961 120 mg BID high, fast (T2DM) vs. PF-06882961 200mg BID (non-diabetic obesity)<br>PF-06882961 200mg BID (T2DM) vs. PF-06882961 200mg BID (non-diabetic obesity) |
| 3 | PF-06882961 80 mg BID low, slow (T2DM) vs. Placebo (T2DM)<br>PF-06882961 80 mg BID high, slow (T2DM) vs. Placebo (T2DM)<br>PF-06882961 120 mg BID low, fast (T2DM) vs. Placebo (T2DM)<br>PF-06882961 120 mg BID high, fast (T2DM) vs. Placebo (T2DM)<br>PF-06882961 200mg BID (T2DM) vs. Placebo (T2DM)<br>PF-06882961 200mg BID (non-diabetic obesity) vs. Placebo (non-diabetic obesity) |
| 4 | PF-06882961 120 mg BID low, fast (T2DM) vs. PF-06882961 80 mg BID high, slow (T2DM)<br>PF-06882961 120 mg BID high, fast (T2DM) vs. PF-06882961 80 mg BID low, slow (T2DM)<br>Placebo (T2DM) vs. Placebo (non-diabetic obesity) |

95% confidence intervals will also be presented for the comparison. No adjustment for multiplicity will be used.

TEAEs of interest will also be presented graphically based on the tabular information from above. The TEAEs will be presented in a two-panel plot, the left panel will give the proportions of TEAEs observed in a treatment group of PF-06882961 and separately the other treatment group of comparison (either another treatment group of PF-06882961 or placebo) while the right panel will display the 95% confidence interval for the risk differences for each TEAE. A vertical line corresponding to the value of 0 will be added to the right-hand plot. Each panel will be paged by treatment group of PF-06882961 and the comparison group.

For the above outputs, footnotes will be included on the tables to provide proper interpretation of confidence intervals and to describe how the comparison was conducted, e.g. “Confidence intervals are not adjusted for multiplicity. 95% Confidence intervals are provided to help gauge the precision of the estimates for Risk Difference.”

#### 6.1.1.2.3. Individual profile plot of adverse events of interest over time

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 (up to and including the Week 13-14 visit [V10]) and the bars will be coloured 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.

#### 6.1.1.2.4. Incidence of first occurrence of adverse events of interest by week

The number and percentage of participants who experience the first occurrence of a TEAE of interest each week (up to and including Week 12) will be tabulated by treatment group and overall and week, where percentage will be defined in two ways. These will be included in the same table and produced separately for each TEAE of interest.

To calculate the percentage each week, the numerator will be the total number of participants with the TEAE of interest that was also their first post-dose occurrence of the event during that respective week. The two approaches for the denominator are: (1) the total overall number of evaluable participants for the respective treatment group; and (2) the total number

of participants who had not discontinued from IP and/or the study for the respective treatment group prior to that respective week (note if a participant did discontinue from IP and/or the study during that respective week they would be included in the denominator).

A figure of the percentage per week will also be produced, with week on the x-axis and a separate line for each treatment group. The percentage will represent the above definition (2) of the denominator but based on blinded data reviews this figure may be adapted or additionally produced based on definition (1). These figures will be produced separately for each TEAE of interest.

#### 6.1.1.2.5. Prevalence of adverse events of interest by week

The number and percentage of participants who are experiencing a TEAE of interest each week (up to and including Week 12) will be tabulated by treatment group and week and overall. A separate table representing the number and percentage by severity (mild, moderate or severe) will also be produced. These tables will be produced separately for each TEAE of interest.

To calculate the percentage each week, the total number of participants who experience the TEAE of interest at any time during the respective week will be the numerator and the total number of participants who had not discontinued from IP and/or the study for the respective treatment group prior to that respective week will be the denominator (note if a participant did discontinue from IP and/or the study during that respective week they would be included in the denominator).

A figure of the overall percentage (i.e. not by severity) per week will be produced, with week on the x-axis and a separate line for each treatment group. A separate figure of the percentage per week will also be produced, with week on the x-axis and a separate line for each severity, paged by treatment group. These figures will be produced separately for each TEAE of interest.

##### 6.1.1.2.5.1. Adverse events of interest during Week 1

An additional summary table (as per Section 5.2.2) of the incidence and severity of TEAEs of interest reported during the first week of treatment will be produced. In these tables, treatment groups with the same Week 1 dose (i.e. 5 mg BID or 10 mg BID) and population (i.e. T2DM or non-diabetic obesity) will be pooled and placebo will be included as two separate groups in this table along with an overall group.

#### 6.1.1.2.6. Time to first occurrence/recurrence of adverse events of interest

Time to the first occurrence of TEAEs of interest will be produced using Cumulative Incidence Plots as described in Section 5.2.4. Participants who discontinue from the study, discontinue from IP or initiate glycemic rescue medication prior to the start of the TEAE of interest 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.

#### 6.1.1.2.7. Time to discontinuation from IP due to Gastrointestinal Disorders AEs

Exploratory summaries on the time to discontinuation from IP (regardless of study discontinuation or continuation) due to Gastrointestinal Disorders AEs (defined as based on System Organ Class) will be produced with a Cumulative Incidence Plot as described in Section 5.2.4. Participants who discontinue will be censored at the associated discontinuation date. There will be a separate line for each treatment group.

#### 6.1.1.2.8. Subset reporting interval

The number and percentage of TEAEs of interest defined based on the subset reporting interval (described in Section 3.5.1.2) will be summarized by treatment group and overall. A separate table representing the number and percentage by severity (mild, moderate or severe) will also be produced. These tables will be produced separately for each TEAE of interest.

#### 6.1.1.2.9. Hypoglycemic Adverse Events

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

CCI [redacted]

### 6.2. Secondary Endpoint(s)

### 6.2.1. Change from Baseline in FPG at Weeks 2, 4, 6, 8, 10 and 12 in participants with T2DM

#### 6.2.1.1. Main Analysis

In all cases the Estimand Set 1A as specified in Section 4 will be utilized, which notably will only include T2DM participants.

Absolute values and changes from baseline in FPG will be summarized descriptively by treatment group and time point as described in Section 5.2.1. Tables will present all data from the screening (visit 1, absolute tables only), beginning of the placebo run-in (visit 2, absolute tables only), baseline and post-baseline time points (including follow-up, which will be restricted to participants who completed 12 weeks of treatment and did not initiate glycemic rescue medication). Box and whisker plots of absolute values and changes from baseline will also be separately produced.

The analysis will be an MMRM (as described in Section 5.2.3) applied to the change from baseline at Weeks 2, 4, 6, 8, 10 and 12 that will be used to estimate the treatment effect related to the secondary Estimand 1A (as described in Section 2.1.2).

The following results from the above primary analysis will be plotted:

- Profile plots of the LSMeans (including 90% confidence intervals) over time, with a separate line for each treatment group
- Profile plots of the LSMean differences to Placebo (including 90% confidence intervals) over time, with a separate line for each treatment group of PF-06882961

Standard SAS output will be provided to support the main statistical summary table for the secondary analysis model but will not be included in the CSR.

Statistical Model Diagnostics

The presence of outliers will be investigated for this analysis. An outlier will be defined as any response data value with a studentized (conditional) residual greater than 3, or less than -3. A listing will be presented of any participants meeting these criteria and will be included with standard SAS outputs. The assumptions of normality will be verified graphically using residual plots. For each fitted model, a set of conditional studentized residual plots will be produced, including residual plot, histogram of normality, QQ plot and summary of fit statistics. The residual plots will not be included in the clinical study report.

If there are outliers or major deviations from normality, then the effect of these on the conclusions may be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

### 6.2.2. Change from Baseline in HbA1c at Weeks 2, 4, 6, 8, 10 and 12 in participants with T2DM

#### 6.2.2.1. Main Analysis

In all cases the Estimand Set 1A as specified in Section 4 will be utilized, which notably will only include T2DM participants.

The summaries and analysis for HbA1c will be similar to that for FPG, as specified in Section 6.2.1.1 to estimate the treatment effect related to the secondary Estimand 2A (as described in Section 2.1.2).

### 6.2.3. Change from Baseline for Body Weight at Weeks 2, 4, 6, 8, 10 and 12 in participants with T2DM

#### 6.2.3.1. Main Analysis

In all cases the Estimand Set 1A as specified in Section 4 will be utilized, which notably will only include T2DM participants.

The summaries and analysis for body weight will be similar to that for FPG, as specified in Section 6.2.1.1 to estimate the treatment effect related to the secondary Estimand 3A (as described in Section 2.1.2)

#### 6.2.3.2. Supplementary Analyses

The percent change from baseline in body weight at Weeks 2, 4, 6, 8, 10 and 12 will additionally be summarized and analyzed as per Section 6.2.1.1.

For the MMRM model, all body weight values (including baseline) will be $\log_e$-transformed prior to analysis (i.e. the outcome in the model will be the difference of the $\log_e$ absolute value at the time point of interest minus the $\log_e$ baseline). All LSMeans and LSMean differences (including confidence intervals) will be back-transformed to give geometric LSMeans and ratios of geometric LSMeans.

The percent change will then be calculated as follows:

Percent change = 100*(back-transformed LSMean – 1)

### 6.2.4. Change from baseline in body weight at Weeks 2, 4, 6 8, 10 and 12 in non-diabetic participants with obesity

#### 6.2.4.1. Main Analysis

In all cases the Estimand Set 1B as specified in Section 4 will be utilized, which notably will only include non-diabetic participants with obesity.

The summaries and analysis for body weight will be similar to that for FPG, as specified in Section 6.2.1.1 to estimate the treatment effect related to the secondary Estimand 3B (as described in Section 2.1.2).

#### 6.2.4.2. Supplementary Analysis

Similar supplementary analyses of the percent change from baseline in body weight as described in Section 6.2.3.2 will be performed using the Estimand Set 1B.

## 6.3. Other Endpoint(s)

### 6.3.1. Pharmacokinetic Endpoints

PF-06882961 concentrations will be characterized by $C_{trough}$ and will be summarized by treatment and by time point using the following descriptive statistics: number of subjects contributing at each time point, arithmetic mean, median, minimum, maximum, Q1, Q3, standard deviation, geometric mean, and geometric CV (%).

Median $C_{trough}$ versus time point will be plotted by dose including error bars representing the inter-quartile range (i.e. Q1 to Q3).

$C_{trough}$ values from PK samples that were collected after discontinuation of investigational product will be listed but excluded from summarization.

PF-06882961 concentrations assessed during random collection (i.e. ~2-6 hours post-dose and unplanned measurements) will only be listed (and not summarized); these data are noted for use in supplemental population-PK analyses as required.

In addition, as permitted by data and determined by the sponsor, PK-PD relationship between plasma concentrations of PF-06882961 and effect on primary, secondary and tertiary endpoints may be characterized using a population PK-PD approach. The objective of such an analysis, if conducted, would aim to explore potential demographic determinants (eg, age, gender, and weight) influencing the observed PK or PD variability in response to PF-06882961. The population PK-PD analysis, if conducted, will be reported separately from the main CSR.

### 6.3.2. Change from Baseline in FPG at Weeks 2, 4, 6, 8, 10 and 12 in non-diabetic participants with obesity

In all cases the Estimand Set 1B as specified in Section 4 will be utilized, which notably will only include non-diabetic participants with obesity.

The summaries and analysis will be similar to that for FPG, as specified in Section 6.2.1.1 to estimate the treatment effect related to the Estimand 1B (as described in Section 2.1.3).

### 6.3.3. Change from Baseline in HbA1c at Weeks 2, 4, 6, 8, 10 and 12 in non-diabetic patients with obesity

In all cases the Estimand Set 1B as specified in Section 4 will be utilized, which notably will only include non-diabetic participants with obesity.

The summaries and analysis for HbA1c will be similar to that for FPG, as specified in Section 6.2.1.1 to estimate the treatment effect related to the Estimand 2B (as described in Section 2.1.3).

## 6.4. Subset Analyses

N/A

## 6.5. Baseline and Other Summaries and Analyses

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

### 6.5.1. 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): age; gender; race; ethnicity; height; weight; body mass index; duration of T2DM (for T2DM participants only); HbA1c; fasting plasma glucose; systolic blood pressure; diastolic blood pressure; pulse rate; eGFR and duration of metformin & total daily dose (for T2DM participants only).

### 6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition for each phase of the study (double-blind treatment and follow-up) and will additionally show which participants were

analyzed for efficacy (Estimand Set 1A and 1B) as well as for safety. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment group and overall.

A summary table of important protocol deviations (IPDs) will be produced by treatment group and overall. An additional summary table restricted to coronavirus disease 2019 (COVID-19) related IPDs only will also be produced if such deviations occur. Listings related to both tables will be produced regardless of whether such deviations occur or not.

### 6.5.3. Banked Biospecimens

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

### 6.5.4. 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.

A separate table listing the use of rescue medication will be produced according to current sponsor reporting standards. The use of rescue medication (grouped by class of medication) will be summarized descriptively by treatment group and overall as described in Section 5.2.2. The classes will be defined based on medications used in the study.

### 6.5.5. Treatment Compliance

A summary table of treatment compliance (by treatment group and overall) will be produced according to current sponsor reporting standards.

### 6.5.6. 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, where an additional table summarizing participant discontinuations due to adverse events for each system organ class and preferred term will be produced by treatment group and overall also.

Exploratory summaries on the time to discontinuation from the study and time to discontinuation from IP (regardless of study discontinuation or continuation) will be produced separately using Cumulative Incidence Plots as described in Section 5.2.4. For both, participants who discontinue from the study/IP will be censored at the associated discontinuation date.

## 6.6. Safety Summaries and Analyses

### 6.6.1. Adverse Events

Described in Section 6.1.1.

### 6.6.2. Laboratory Data

Laboratory data from will be listed and summarized by treatment group and overall, in accordance with the sponsor reporting standards.

Baseline is as defined in Section 3.

#### 6.6.2.1. Focused Laboratory Summaries on Endpoints of Interest

Absolute values, changes from baseline and percent changes from baseline in calcitonin, amylase, lipase, TSH, free T4, lipid profile, liver function tests (i.e. ALT, AST, alkaline phosphatase, total bilirubin, bile acids and GGT) and eGFR (as outlined in Section 3.5.3.1) will be summarized by treatment and time point as per Section 5.2.1 (unplanned readings will not be included in these summaries). Follow-up data will be included in the summaries with data from all participants in the safety analysis set. Tables will be paged by parameter. Baseline is as defined in Section 3.

The following box and whisker plots for each parameter will be produced:

- Absolute values over time by treatment
- Change from baseline over time by treatment
- Percentage change from baseline over time by treatment

MMRM models (as described in Section 5.2.3) will be applied to the change from baseline at Weeks 2, 4, 6, 8, 10 and 12 (as applicable) for each parameter (except triglyerides, ALT, AST, Alkaline Phosphatase and GGT) and population (T2DM or non-diabetic participants with obesity) separately using the safety analysis set (as defined in Section 4). From each model, the LSMeans together with 90% confidence intervals, standard errors and p-values will be obtained for each treatment group at each time point. Differences in LSMeans between each treatment group of PF-06882961 relative to placebo (from the same population as restricted within the model) at each time point, together with 90% confidence intervals, standard errors and 2-sided p-values will also be obtained. A plot of the LSMean differences to Placebo (including 90% confidence intervals) over time, with a separate line for each treatment group of PF-06882961 will be produced separately for each parameter and population. Standard SAS outputs will be provided to support the main statistical summary tables but will not be included in the CSR.

Additionally, MMRM models will be applied to the percent changes from baseline in Triglycerides, ALT, AST, Alkaline Phosphatase and GGT for each parameter and population (T2DM or non-diabetic participants with obesity) separately. Similar to 6.2.3.2, the $\log_e$ changes from baseline will be modelled and results will be back-transformed for reporting. Similar outputs to the absolute change from baseline MMRM models described above will be genearated (including plots of LSMean differences to placebo).

After review of unblinded tables, if MMRM diagnostics reveal that any residuals deviate substantially from a normal distribution that, for example, require log transformation, the

MMRM model will be updated as necessary (e.g. apply log transformation and report modelled percent change from baseline).

#### 6.6.2.2. Clinical Laboratory Parameters of Interest

An additional summary table of the number of participants (from the Safety Analysis Set as defined in Section 4) with "Flag Level" or "Alert Level" abnormalities for each of the clinical laboratory parameters of interest as specified in Section 3.5.3.2 will be produced. This table will summarise the number of participants with "Flag level" or "Alert level" abnormalities separately and by treatment group, placebo run-in and overall (i.e. post-dose) as per Section 5.2.2.

### 6.6.3. Vital Signs

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 including the two placebo groups.

MMRM models (as described in Section 5.2.3) will be applied to the change from baseline at Weeks 0 (2H only), 2, 4, 6 (0 and 2H separately), 8, 10 and 12 (0 and 2H separately, as applicable) for supine systolic and diastolic blood pressure and pulse rate and population (T2DM or non-diabetic participants with obesity) separately using the safety analysis set (as defined in Section 4). From each model, the LSMeans together with 90% confidence intervals, standard errors and p-values will be obtained for each treatment group at each time point. Differences in LSMeans between each treatment group of PF-06882961 relative to placebo (from the same population as restricted within the model) at each time point, together with 90% confidence intervals, standard errors and 2-sided p-values will also be obtained. A plot of the LSMean differences to Placebo (including 90% confidence intervals) over time, with a separate line for each treatment group of PF-06882961 will be produced separately for each parameter and population. Standard SAS outputs will be provided to support the main statistical summary tables but will not be included in the CSR.

Participants with absolute values and changes from baseline for vital signs (over all post-dose measurements) meeting categories as defined in the Appendix 5 will also be summarized descriptively by treatment group and overall. 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.

### 6.6.4. Electrocardiograms

Average of the triplicate measurements (where applicable) will be used in analyses. Absolute values and changes from baseline in QT, heart rate, QTcF, 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, 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 including the two placebo groups.

MMRM models (as described in Section 5.2.3) will be applied to the change from baseline at Weeks 0 (2H only), 2, 4, 6 (0 and 2H separately), 8, 10 and 12 (0 and 2H separately, as applicable) for QT, heart rate and QTcF and population (T2DM or non-diabetic participants with obesity) separately using the safety analysis set (as defined in Section 4). From each model, the LSMeans together with 90% confidence intervals, standard errors and p-values will be obtained for each treatment group at each time point. Differences in LSMeans between each treatment group of PF-06882961 relative to placebo (from the same population as restricted within the model) at each time point, together with 90% confidence intervals, standard errors and 2-sided p-values will also be obtained. A plot of the LSMean differences to Placebo (including 90% confidence intervals) over time, with a separate line for each treatment group of PF-06882961 will be produced separately for each parameter and population. Standard SAS outputs will be provided to support the main statistical summary tables but will not be included in the CSR.

Participants with ECG endpoints and changes from baseline (QTcF, PR and QRS) meeting categories as defined in the Appendix 5 (for QTcF these correspond to the Pfizer Guidance [3]) will also be summarized descriptively by treatment group and overall. 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.

### 6.6.5. Assessment of Mental Health

C-SSRS data (mapped to C-CASA scores as described in Section 3.5.6) using the safety population defined in Section 4, will be summarized categorically by treatment and time point as outlined in Section 5.2.2 (which will include screening data).

PHQ-9 data (responses to each of the 9 items) using the safety population defined in Section 4, will be summarized categorically for each question separtely by treatment and time point as outlined in Section 5.2.2. The PHQ-9 total score (as defined in Section 3.5.6) will additionally be summarized descriptively by treatment group and time point as outlined in Section 5.2.1.

The number of participants who met the criteria for referral to a mental health professional will be listed and summarized by treatment group and time point as outlined in Section 5.2.2.

### 6.6.6. Physical Examination

All physical examination data will be provided in a listing using sponsor reporting standards.

## 7. INTERIM ANALYSES

### 7.1. Introduction

*No formal interim analysis will be conducted for this study. However, 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 PK/PD modeling, and/or supporting clinical development. If such an unblinded review is deemed necessary, the decision for the sponsor to conduct the review will be documented along with details on plans to control dissemination.*

### 7.2. Interim Analyses and Summaries

Not applicable.

## 8. REFERENCES

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

2. Blyth CR, Still HA. Binomial confidence intervals. Journal of the American Statististical Association. 78:108-116, 1983, & Casella G. Refining binomial confidence intervals. The Canadian Journal of Statistics, 14:113-129, 1986

3. 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.

# 9. APPENDICES

## Appendix 1. Summary of Efficacy Analyses

| Endpoint | Analysis Type | Population | Data Inclusion and Rules for Handling Intercurrent Events and Missing Data | Analysis Model |
|---|---|---|---|---|
| Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 10 and 12 | Summary | Estimand Set 1A | GRM: Censor all values post first use<br>DFI: Censor all values post discontinuation<br>MV: Not imputed | N/A |
| | Main analysis | | | MMRM |
| Change from baseline in FPG at Weeks 2, 4, 6, 8, 10 and 12 | Summary | | | N/A |
| | Main analysis | | | MMRM |
| Change from baseline in Body Weight at Weeks 2, 4, 6, 8, 10 and 12 | Summary | | | N/A |
| | Main analysis | | | MMRM |
| Percent change from baseline in Body Weight at Weeks 2, 4, 6, 8, 10 and 12 | Summary | | | N/A |
| | Main analysis | | | MMRM |
| Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 10 and 12 | Summary | Estimand Set 1B | DFI: Censor all values post discontinuation<br>MV: Not imputed | N/A |
| | Main analysis | | | MMRM |
| Change from baseline in FPG at Weeks 2, 4, 6, 8, 10 and 12 | Summary | | | N/A |
| | Main analysis | | | MMRM |
| | Summary | | | N/A |

| | | | | |
|---|---|---|---|---|
| Change from baseline in Body Weight at Weeks 2, 4, 6, 8, 10 and 12 | Main analysis | | | MMRM |
| Percent change from baseline in Body Weight at Weeks 2, 4, 6, 8, 10 and 12 | Summary | | | N/A |
| | Main analysis | | | MMRM |

Abbreviations: DFI = discontinuation from IP; GRM = glycemic rescue medication; MV = missing values (note this includes missing values produced through censoring).

## Appendix 2. Statistical Methodology Details

Example SAS code for MMRM Model (strata for gender included):

```
proc mixed data = dataset method=reml;
        class subject treatment time strata;
        model cfb = treatment base time base*time time*treatment strata / 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 3. Data Set Descriptions

To explore the data further and to assess the goodness-of-fit of all statistical models, separate SAS datasets and .CSV files will be provided by the clinical programmer to the statistician.

The dataset requirements for the Dataset (Snapshot PD Dataset, SNAP_PD) are specified in the table below. Note, the variable names and labels are suggested labels only and the actual names and labels and code levels should be consistent with current sponsor reporting standards:

| Suggested Variable Name | Suggested Variable Label | Specifications | Order in the dataset |
|---|---|---|---|
| USUBJID | Unique Subject ID | | 1 |
| Treattxt | Treatment Label | | 2 |
| Leg_sort | Treatment Code | | 3 |
| Dose | Dose (mg) | Expected dose based on titration scheme (taken from Figure 1 from protocol) | 4 |
| Site | Site | | 5 |
| Age | Age | Age | 6 |
| Agecat | Age Category | 1 = <18.<br>2 = 18 – 44,<br>3 = 45 – 64,<br>4 = >=65 | 7 |

| Suggested Variable Name | Suggested Variable Label | Specifications | Order in the dataset |
|---|---|---|---|
| Gender | Gender | 1 = Female<br>2 = Male | 8 |
| Height | Height | Height | 9 |
| Weight_Screen | Weight (Screening) | Weight (Screening value) | 10 |
| Race | Race | Race | 11 |
| Strata | Strata | 1 = Female<br>0 = Male | 12 |
| Time point | Time point (weeks) | Time point (in weeks) | 13 |
| Rescue | Glycemic Rescue Medication | 1 = Started using glycemic rescue medication<br>0 = Not started glycemic rescue medication | 14 |
| HbA1c | HbA1c | HbA1c value | 15 |
| HbA1c_bas | Baseline (HbA1c) | Baseline for HbA1c | 16 |
| FPG | Fasting Plasma Glucose | Fasting Plasma Glucose value | 17 |
| FPG_bas | Baseline (Fasting Plasma Glucose) | Baseline for Fasting Plasma Glucose | 18 |
| Weight | Body Weight | Body Weight value | 19 |
| Weight_bas | Baseline (Body Weight) | Baseline for Body Weight | 20 |

## Appendix 4. List of Abbreviations

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| BLQ | below the limit of quantitation |
| CI | confidence interval |
| $C_{trough}$ | Trough concentrations (i.e., measured concentration at the end of a dosing interval), to be directly read from pre-dose concentrations. |
| C-CASA | Columbia-Classification Algorithm of Suicide Assessment |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| COVID-19 | Coronavirus disease 2019 |
| CSR | clinical study report |
| CCI | [redacted] |
| ECG | Electrocardiogram |
| FPG | fasting plasma glucose |
| GGT | gamma-glutamyl transferase |
| ICH | International Council for Harmonisation |
| IPD | Important protocol deviation |
| LS | least-squares |
| LSM | least-squares mean |
| MAR | missing at random |
| MMRM | mixed model repeated measures |
| N/A | not applicable |
| CCI | [redacted] |
| PD | pharmacodynamic(s) |
| PHQ-9 | Patient Health Questionnaire-9 |
| PK | pharmacokinetic(s) |
| PT | preferred term |
| QTcF | corrected QT (Fridericia method) |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SOA | Schedule of Activities |
| TEAE | treatment emergent adverse event |
| CCI | [redacted] |

## Appendix 5. 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 6. C-SSRS Mapped to C-CASA - Suicidal Ideation and Behavior Events and Codes

### C-SSRS Mapped to C-CASA (Suicidality Events and Codes)

| Event Code | C-CASA Event | C-SSRS Response |
|---|---|---|
| Suicidal Ideation | | |
| 1 | Passive | "Yes" on "Wish to be dead" |
| 2 | Active: Nonspecific (no method, intent, or plan) | "Yes" on "Non-Specific Active Suicidal Thoughts" |
| 3 | Active: Method, but no intent or plan | "Yes" on "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act" |
| 4 | Active: Method and intent, but no plan | "Yes" on "Active Suicidal Ideation with Some Intent to Act, without Specific Plan" |
| 5 | Active: Method, intent, and plan* | "Yes" on "Active Suicidal Ideation with Specific Plan and Intent" |
| Suicidal Behavior | | |
| 1 | Completed suicide | "Yes" on "Completed Suicide" |
| 2 | Suicide attempt | "Yes" on "Actual Attempt" |
| 3 | Interrupted attempt | "Yes" on "Interrupted attempt" |
| 4 | Aborted attempt | "Yes" on "Aborted attempt" |
| 5 | Preparatory actions toward imminent suicidal behaviors | "Yes" on "Preparatory Acts or Behavior" |
| Self-injurious behavior, no suicidal intent | | |
| | Self-injurious behavior, no suicidal intent | "Yes" on "Has subject engaged in Non-suicidal Self-Injurious Behavior?" |

*According to C-SSRS, the definition of *plan* includes intent (i.e., intent to complete the suicide is implicit with the concept of plan). Thus, there is no need for the category *method and plan, but no intent*.