Protocol C3991004

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, DOSE RANGING, DOSE FINDING, PARALLEL GROUP STUDY TO ASSESS EFFICACY AND SAFETY OF PF-07081532, AND OPEN LABEL ORAL SEMAGLUTIDE, IN ADULTS WITH TYPE 2 DIABETES MELLITUS (T2DM) INADEQUATELY CONTROLLED ON METFORMIN, AND SEPARATELY PF-07081532 COMPARED TO MATCHING PLACEBO IN ADULTS WITH OBESITY BUT WITHOUT T2DM

Statistical Analysis Plan

(SAP)

Version: 3

Date: 27SEP2023

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 26APR2023	Original 21SEP2022	N/A	N/A

2
16AUG2023
	Original
	21SEP2022
		Analysis reduction due to program termination	Planned analyses were reduced in scope to align with study and program reporting needs following study termination:
			• MMRM analyses are limited to the following (Sections 3.1, 3.2, and 5.2.2):
			  • Primary endpoint for Cohort 1 (T2DM): placebo-adjusted, change from baseline in **HbA1C** (%) at Week 32 for Cohort 1 (T2DM)
			  • Primary endpoint for Cohort 2 (Obesity): placebo-adjusted, percent change from baseline in **body weight** (kg) at Week 32 for Cohort 2 (Obesity)
			  • Secondary endpoint for Cohort 1 (T2DM): placebo-adjusted, percent change from baseline in **body weight** (kg) at Week 32 for Cohort 1 (T2DM)
			• MMRM will be limited to visits up to and including Week 16 for Cohort 1 (T2DM) and Week 20 for Cohort 2 (Obesity)
			• Extension population and analyses of Extension data have been removed
			• Box plots planned for continuous endpoints were removed and will not be produced (previously included in Sections 4,5.2, 5.2.1, 5.2.2, 6.1.1, 6.2.1.1, 6.2.2.1, and 6.4)

			• Endpoints defined as categories of continuous endpoints (Section 3.2 and 6.2.1.1) will not be summarized nor modeled. These endpoints will not be summarized but will be derived and included in the ADaM datasets:
			
			  • Proportion of participants who achieve HbA1C <7% (<53 mmol/mol) at Week 32
			
			  • Proportion of participants achieving ≥5%, ≥10%, and ≥15% body weight loss at Week 32 relative to baseline

			CCI [redacted]
			• Plots of vital sign and ECG data will not be produced • 3 Tier Aes and AESIs will not be summarized separately from standard AE reporting

3 27SEP2023	Original 21SEP2022	Analysis clarifications	• In Section 5.2.2, MMRM models have been updated to include a baseline*time interaction term • Conventions for handling non-fasting lab values and values below the level of quantification have been added to Section 3.5.2 • Spaghetti plots of Total Bile Acids (TBA) have been added in Section 6.8.2 • Summary of recurrence of TEAEs has been added to Section 6.8.1 • Fasting glucagon was removed from Section 6.7.1 • QT has been added as an ECG parameter and ECG listings have been added to Section 6.8.4

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3991004. 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. Modifications to the Analysis Plan Described in the Protocol

Due to termination of the PF-07081532 program and premature termination of study C3991004:

- Planned analyses were modified or reduced to align with the updated planned study report;
- MMRM models have been updated to include a baseline*time interaction term
- These changes will not be reflected in a protocol amendment.

2.2. Study Objectives, Endpoints, and Estimands

Table 2. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To evaluate the efficacy of a range of PF-07081532 doses compared to placebo, ***in participants with T2DM inadequately controlled on metformin***	Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32	**Population:** All treated participants with T2DM inadequately controlled on metformin **Variable:** Placebo-adjusted, change from baseline in **HbA1C** at Week 32 **Intercurrent events:** • An On Treatment strategy will be used: Measurements after initiation of glycemic rescue medication or discontinuation of study intervention are considered as intercurrent events, which will be censored and treated as missing data. The missing data due to censoring, study withdrawal or other reasons (e.g., laboratory failure) will have data imputed based on a MAR assumption. Participants with inadequate compliance will have their HbA1C values used as-is in the analysis **Population-level summary measure:** The population-based treatment effect will be the difference in the mean change from baseline in each PF-07081532 arm compared to placebo
To evaluate the efficacy of a range of PF-07081532 doses compared to placebo, ***in participants with obesity but without T2DM***	Placebo-adjusted, percent change from baseline in ***body weight*** at Week 32	**Population:** All treated participants with obesity but without T2DM **Variable**: Placebo-adjusted, percent change from baseline in body weight at Week 32 **Intercurrent events:** • An On Treatment strategy will be used: Measurements after discontinuation of study intervention are considered as intercurrent events, which will be censored and treated as missing data. The missing data due to censoring, study withdrawal or other reasons (e.g., equipment failure) will have data imputed based on a MAR assumption. Participants with inadequate compliance will have their body weight values used as-is in the analysis

Table 2. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
		Population-level summary measure: The population-based treatment effect will be the difference in the mean percent change from baseline in each PF-07081532 arm compared to placebo
Secondary:	**Secondary:**	**Secondary:**
To assess the effect of a range of PF-07081532 doses compared to placebo on various parameters, ***in participants with T2DM inadequately controlled on metformin***	Proportion of participants who achieve ***HbA1C*** <7% (<53 mmol/mol) at Week 32	**Population:** All treated participants with T2DM inadequately controlled on metformin **Variable**: Proportion of participants who achieve HbA1C <7% (<53 mmol/mol) at Week 32 **Intercurrent events:** • An On Treatment strategy will be used: Measurements after initiation of glycemic rescue medication or discontinuation of study intervention are considered as intercurrent events which will be censored and treated as missing data. Missing data will not be imputed. Participants with inadequate compliance will have their HbA1C values used as-is in the analysis. **Population-level summary measure:** The population-based treatment effect will be the odds ratio of achieving HbA1c < 7% in a PF-07081532 arm relative to placebo
	Placebo-adjusted, change from baseline in ***FPG*** at Week 32	The estimand for placebo-adjusted, change from baseline in ***FPG*** at Week 32 endpoint will be constructed in a similar manner as Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32
	Placebo-adjusted, percent change from baseline in ***body weight*** at Week 32	The estimand for the placebo-adjusted, percent change from baseline in ***body weight*** at Week 32 endpoint will be constructed in a similar manner as Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32
To compare the efficacy of PF-07081532 and Rybelsus relative to placebo, ***in participants with T2DM inadequately controlled on metformin***	Placebo-adjusted, change from baseline in ***HbA1C*** at Week 32	**Population:** All treated participants with T2DM inadequately controlled on metformin **Variable:** Placebo-adjusted, change from baseline in **HbA1C** at Week 32 **Intercurrent events:** • An On Treatment strategy will be used: Measurements after initiation of glycemic rescue medication or discontinuation of study intervention are considered as intercurrent events, which will be censored and treated as missing data.

Table 2. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
		The missing data due to censoring, study withdrawal or other reasons (eg, laboratory failure) will have data imputed based on a MAR assumption. Participants with inadequate compliance will have their HbA1C values used as-is in the analysis **Population-level summary measure:** The population-based treatment effect will be the difference in the mean change from baseline in each PF-07081532 arm and Rybelsus arm compared to placebo
To assess the effect of a range of PF-07081532 doses compared to placebo on various parameters ***in participants with obesity but without T2DM***	• Proportion of participants achieving ≥5%, ≥10%, and ≥15% ***body weight loss*** at Week 32 relative to baseline • Placebo-adjusted, ***absolute*** change from baseline in ***waist circumference*** at Week 32 • Placebo-adjusted, ***absolute*** change from baseline in ***waist-to-hip ratio*** at Week 32 • Placebo-adjusted, change from baseline in ***HOMA-IR*** at Week 32 • Placebo-adjusted, change from baseline in ***HOMA-S*** at Week 32	**Population:** All treated participants with obesity but without T2DM **Variables:** Proportion of participants achieving ≥5%, ≥10%, and ≥15% body weight loss at Week 32 relative to baseline **Intercurrent events:** • An On Treatment strategy will be used: Measurements after initiation of glycemic rescue medication or discontinuation of study intervention are considered as intercurrent events, which will be censored and treated as missing data. Missing data will not be imputed. Participants with inadequate compliance will have their body weight values used as-is in the analysis **Population-level summary measure:** The population-based treatment effect will be the odds ratio of PF-07081532 arm relative to placebo The estimand for each of the continuous endpoints will be constructed in a similar manner as the primary endpoint Placebo-adjusted, percent change from baseline in **body weight** at Week 32

To assess the safety and tolerability with a range of PF-07081532 doses compared to placebo, ***in participants with T2DM inadequately controlled on metformin*** and	In ***each*** population randomized –
	• Number (and percent) of participants with:
	  • TEAEs
	  • SAEs	

Table 2. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
separately ***participants with obesity but without T2DM***	• AE leading to permanent discontinuation from study intervention or study • Hypoglycemia • Clinical laboratory abnormalities • Vital sign abnormalities • 12-lead ECG abnormalities • And TEAEs, presented in descending order of frequency	

Table 2. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
To assess the safety and tolerability with a range of PF-07081532 doses compared to placebo, ***in participants with obesity but without T2DM***	Assessment of mental health as determined by – • C-SSRS	
Tertiary:	**Tertiary:**	**Tertiary:**
CCI [redacted]		

Table 2. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
To characterize PK of – • PF-07081532, ***in participants with T2DM inadequately controlled on metformin*** and separately ***participants with obesity but without T2DM*** • Rybelsus, ***in participants with T2DM inadequately controlled on metformin***	In ***<u>each</u>*** population randomized, descriptive summary of trough concentrations of PF-07081532 and Rybelsus	
CCI		

In all cases, baseline is defined as the evaluable result closest prior to dosing on Day 1/Visit 3

Efficacy assessments will be assessed by the On Treatment estimand. Study termination occurred after the study was fully randomized and prior to any participant achieving Week 32, and thus, efficacy analyses will be limited through Week 16 for Cohort 1 (T2DM) and through Week 20 for Cohort 2 (Obesity).

2.2.1. Primary Estimands

Cohort 1 (T2DM)

The On Treatment strategy estimates the effect if all patients maintain their randomized treatment and adhere to the protocol. It includes the following attributes:

- Treatment condition: The randomized treatment under the scenario where initiation of glycemic rescue medication or discontinuation of study intervention has not occurred. Observations after that will be censored and treated as missing data;
- Population: All treated patients with T2DM inadequately controlled on metformin;
- Variable: Placebo-adjusted, change from baseline in HbA1C at Week 32;
- Population-level summary: Difference of variable means between PF-07081532 and placebo.

Cohort 2 (Obesity)

The On Treatment strategy estimates the effect if all patients maintain their randomized treatment and adhere to the protocol. It includes the following attributes:

- Treatment condition: The randomized treatment under the scenario where initiation of glycemic rescue medication or discontinuation of study intervention has not occurred. Observations after that will be censored and treated as missing data
- Population: All treated patients with obesity but without T2DM;
- Variable: Placebo-adjusted, percent change from baseline in body weight at Week 32;
- Population-level summary: Difference of variable means between PF-07081532 and placebo.

The On Treatment strategy estimates the effect if all patients maintain their randomized treatment and adhere to the protocol. It includes the following attributes:

- Treatment condition: The randomized treatment under the scenario where initiation of glycemic rescue medication or discontinuation of study intervention has not occurred. Observations after that will be censored and treated as missing data;
- Population: All treated patients with T2DM inadequately controlled on metformin;
- Variable: Placebo-adjusted change from baseline in FPG (mg/dL, mmol/L) at Week 32, Placebo-adjusted percent change from baseline in body weight (kg) through Week 32;

- Population-level summary: Difference of variable means between PF-07081532 and placebo.

2.3. Study Design

This is a multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled, dose-ranging, dose-finding, parallel-group study to assess efficacy and safety/tolerability of PF-07081532, and open-label Rybelsus in Cohort 1 (T2DM), and separately PF-07081532 compared to matching placebo in Cohort 2 (Obesity).

The study will employ an IRC who will be responsible for ongoing review of unblinded safety and tolerability according to an IRC Charter. In addition, an interim analysis to assess efficacy and safety/tolerability in the Cohort that achieves PCD early may be performed.

Number of Participants: Approximately 780 participants (60/arm) will be enrolled/randomized across 2 populations in the study.

Study Arms and Duration:

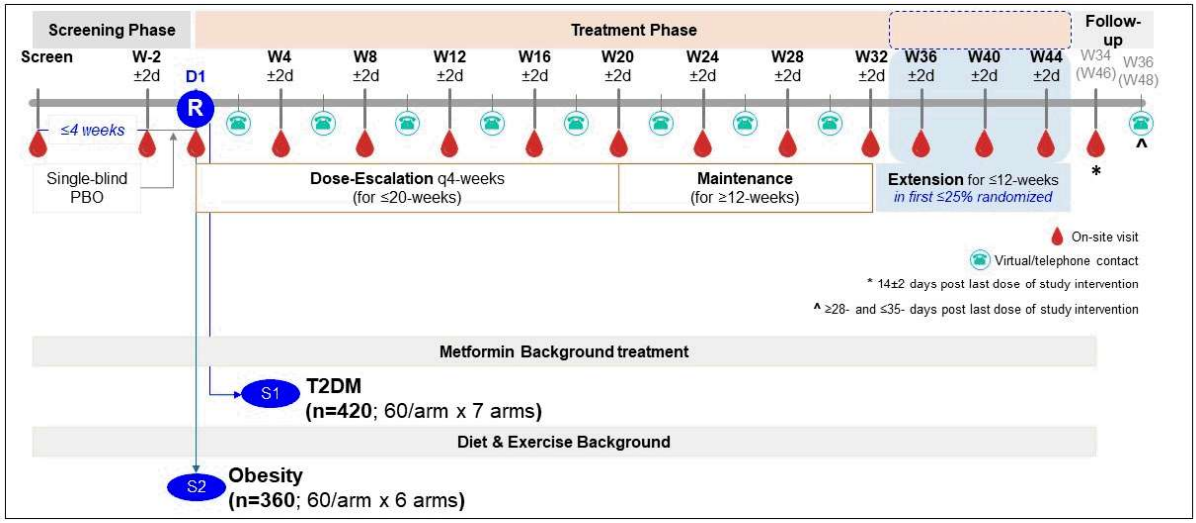
- In **Cohort 1 (T2DM)**, three interventions, PF-07081532, its matching placebo, and open-label Rybelsus, will be evaluated across 7 arms in participants with T2DM on a background of metformin.

- In **Cohort 2 (Obesity)**, two interventions, PF-07081532 and its matching placebo, will be evaluated across 6 arms in participants with obesity.

- The treatment duration in this study will be 32 weeks for most participants; though in the first set of up to 25% randomized participants, treatment interval will extend for an additional up to 12 weeks for a total duration of up to 44 weeks.

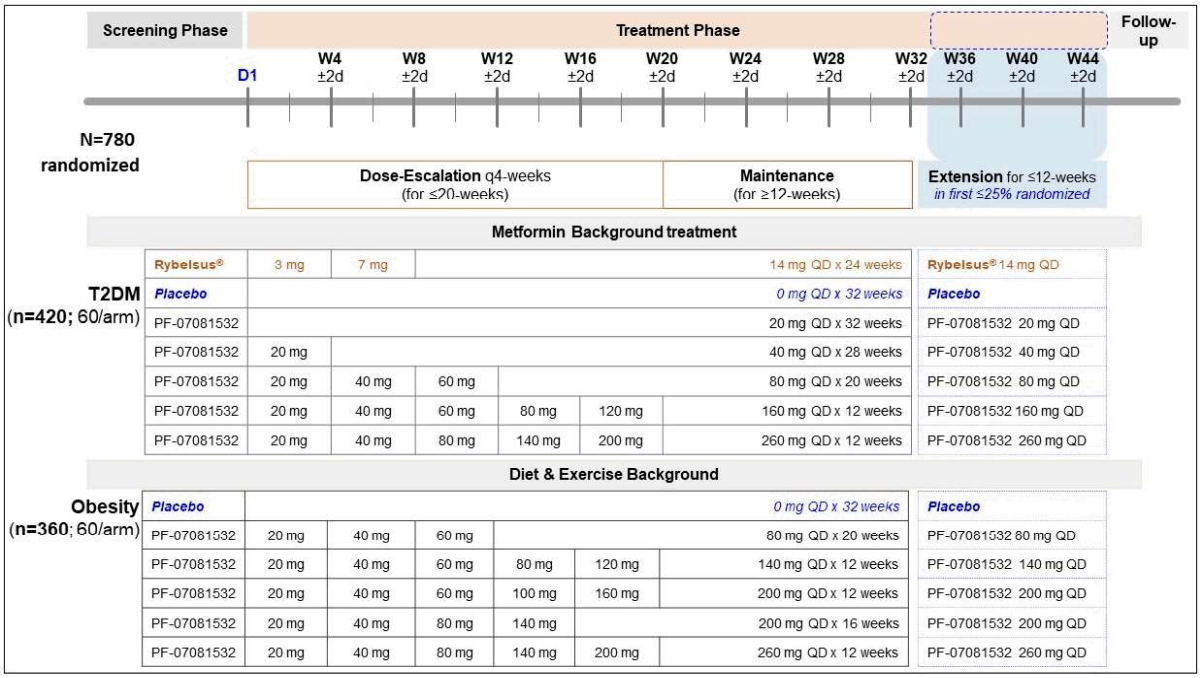
The high-level study design is summarized below.

Figure 1. High Level Study Design



The dose-escalation scheme to be employed is outlined below.

Figure 2. Dose Escalation Scheme



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

In Cohort 1 (T2DM) the primary efficacy endpoint is, the placebo-adjusted, change from baseline in **HbA1C** (%) at Week 32.

In Cohort 2 (Obesity) the primary efficacy endpoint is, the placebo-adjusted, percent change from baseline in **body weight** (kg) at Week 32.

3.2. Secondary Endpoint(s)

Cohort 1 (T2DM)

- Proportion of participants who achieve **HbA1C** <7% (<53 mmol/mol) at Week 32
- Placebo-adjusted, change from baseline in **FPG** (mg/dL, mmol/L) at Week 32
- Placebo-adjusted, percent change from baseline in **body weight** (kg) at Week 32
- Placebo-adjusted, change from baseline in **HbA1C** (%) in the Rybelsus arm at Week 32

Cohort 2 (Obesity)

- Proportion of participants achieving ≥5%, ≥10%, and ≥15% **body weight loss** at Week 32 relative to baseline
- Placebo-adjusted, **absolute** change from baseline in **waist circumference (cm)** at Week 32
- Placebo-adjusted, **absolute** change from baseline in **waist-to-hip ratio** at Week 32
- Placebo-adjusted, change from baseline in **HOMA-IR** at Week 32
  - HOMA-IR is calculated as: ([FPI] × FPG)/405
- Placebo-adjusted, change from baseline in **HOMA-S** at Week 32
  - HOMA-S% is calculated as (22.5/[FPI] × FPG))*100

Safety Endpoints Analyzed in both Cohort 1 (T2DM) and Cohort 2 (Obesity) separately

Number (and percent) of participants with:

- TEAEs
- SAEs
- AE leading to permanent discontinuation from study intervention or study
- Hypoglycemia
- Clinical laboratory abnormalities
- Vital sign abnormalities
- 12-lead ECG abnormalities

Assessment of mental health as determined in Cohort 2 (Obesity) by C-SSRS

CCI

- Descriptive summary of trough concentrations of PF-07081532 and Rybelsus

- Descriptive summary of trough concentrations of PF-07081532 and Rybelsus

3.4. Baseline Variables

In all cases, baseline is defined as the evaluable result closest prior to dosing on Day 1/Visit 3. Baseline measures will be included as a covariate in all applicable statistical models. The statistician may conduct further exploratory analyses into the effect of covariates and factors (such as gender, age and strata) on the efficacy endpoints. If conducted, and considered relevant to the CSR, the methods will be fully justified and discussed within the report.

Focused change from baseline summaries (including both absolute changes from baseline and percent change from baseline, calculated separately) of the following safety laboratory endpoints will be assessed:

- Change from baseline in calcitonin to all post-dose time points as per the 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 hs-CRP to all post-dose time points as per the SOA
- Change from baseline in Urinary Albumin:Creatinine Ratio 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-C, HDL-C and TG) to all post-dose time points as per the SOA
- Change from baseline in liver function tests (ALT, AST, alkaline phosphatase, total bilirubin, and total bile acid) to all post-dose time points as per the SOA
- Change from baseline in eGFR to all post-dose time points as per the SOA

3.5. Safety Endpoints

The safety endpoints included as part of secondary endpoints are listed in the Section 3.2. Some additional details are provided in this section.

3.5.1. Adverse Events

AEs are considered TEAEs relative to a given treatment if the event starts during the effective duration of treatment (i.e. starting on or after the first dose but before the last dose plus lag time).

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

Adverse events occurring during the placebo run-in period (i.e. starting from Day -14, inclusive, up to and before the first dose of active treatment on Day 1) will be considered non-treatment emergent.

3.5.2. 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 abnormality criteria. 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).

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.

Table 3. Laboratory Abnormalities

Parameter	Flag Level	Alert Level	Conventional Units
Amylase	> ULN	-	U/L
Calcitonin	> ULN	-	Ng/L
Lipase	> ULN	-	U/L
HbA1C	-	>10	%
Fasting Plasma Glucose	-	< 70	mg/dL
	-	> 270	mg/dL
	-	>240	mg/dL
Alanine aminotransferase	> ULN	-	U/L
	≥ 2x ULN	-	U/L
	> 3x ULN	-	U/L
	> 5x ULN	>8x ULN	U/L
	> 5x ULN	>10x ULN	U/L
	> 5x ULN	>20x ULN	U/L
Aspartate aminotransferase	> ULN	-	U/L
	≥ 2x ULN	-	U/L
	> 3x ULN	-	U/L
	> 5x ULN	>8x ULN	U/L
	> 5x ULN	>10x ULN	U/L
	> 5x ULN	>20x ULN	U/L
Alkaline Phosphatase	≥ 2x ULN	-	U/L
	> 3x ULN	-	U/L
	>5x ULN	-	U/L
Creatinine	≥0.3 relative to baseline	≥0.4 relative to baseline	mg/dL
Total Bilirubin	≥ 2x ULN	>3x ULN	mg/dL
Direct and Indirect Bilirubin	> ULN	-	mg/dL

All flag level changes are cumulative from baseline (defined as result closest prior to dosing at Visit 3 (Day 1);
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 1 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). In cases where lab results are reported as below the level of quantification, results will be imputed as 0.1 units below the level of quantification.

In cases where fasting status impacts interpretability of results, results will be excluded from summary tables and excluded lab parameters will be stated in a footnote.

3.5.3. Vital Signs Data

Vital sign measurements (blood pressure and pulse rate) will be taken as detailed in the Schedule of Activities given in the protocol. The average of the triplicate measurements collected at each appropriate assessment time will be calculated for each vital sign parameter. Participants randomized to Rybelsus will have a single measurement instead of triplicate measurements and the single measurement will be used as is.

Baseline will be defined as the average of the triplicate measurements at the visit closest prior to dosing at Visit 3 (Day 1).

Changes from baseline for seated SBP and DBP and pulse rate will be calculated for each post baseline measurement.

3.5.4. Electrocardiogram Data

Standard 12-lead ECG (including HR, 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 centrally read tracings collected at each appropriate assessment time will be calculated for each ECG parameter. Participants randomized to Rybelsus will have a single measurement instead of triplicate measurements and the single measurement will be used as is.

Baseline will be defined as the average of the triplicate measurements at the visit closest prior to dosing at Visit 3 (Day 1).

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

3.5.5. Columbia Suicide Severity Rating Scale (C-SSRS) Data

C-SSRS data will be mapped to C-CASA per Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials

The following 3 endpoints will be used for suicidality data analysis and evaluation:

- Suicidal Behavior

- Suicidal Ideation
- Suicidal Behavior or Ideation

Suicidal behavior: A participant is said to have suicidal behavior if the participant has experienced any of the following events (C-CASA event codes 1-3):

- Completed suicide;
- Suicide attempt; or
- Preparatory acts toward imminent suicidal behavior.

Suicidal ideation: Any observed suicidal ideation maps to a single C-CASA category. Depending on the scale used, more granularity of observed ideation (sub-categories of C-CASA category 4) may be displayed. The C-SSRS, for example, includes five ideation questions (that map to C-CASA category 4) with increasing severity.

Suicidal data is collected at screening for two time intervals. Any suicidal ideation at any point in lifetime as well as suicidal ideation within the past year or suicidal behavior within the last 5 years. Baseline/day of randomization includes details of suicidality since the screening assessment, and study visits post-baseline includes details of suicidality since the previous visit.

A participant listing of C-CASA categories as well as the underlying scale data will be provided. In addition, a summary table with the number and percent of participants with a positive response within each C-CASA category by treatment group at screening, baseline, and at any time post-baseline will be provided.

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.

Participants who are randomized to the wrong cohort, in error, will have the incorrect cohort assignment remain in Impala 2.0 but the clinical database will include the correct cohort. As the treatment groups are not the same for the two cohorts, participants cannot be analyzed as treated; participants will be analyzed as randomized.

Participants enrolled in the same study multiple times will be reported and documented as a protocol deviation. Data for applicable participants will be excluded for all planned efficacy and safety analyses unless decided otherwise upon clinical review. Blinded participant safety data will be listed for the clinical review, and a data reporting decision will be made before the database release

The analysis populations for reporting are below:

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

Table 4. Analysis Sets

Population	Description
Enrolled	All participants who sign the ICD **and** are randomized • A participant will be considered enrolled if informed consent is not withdrawn prior to participating in any study activity; • 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
Randomly assigned to investigational product	All participants randomly assigned to study intervention regardless of whether or not study intervention was administered.
Evaluable	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the randomized 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	All participants randomly assigned to study intervention and who take at least 1 dose of PF-07081532 or Rybelsus and in whom at least one concentration value is reported.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

This study was terminated prior to observation of Week 32, and prior to reaching a maintenance dose in most participants. Statistical analyses will be limited to visits with sufficient data and interpretation may be limited.

For each cohort separately, statistical inference will be based on the primary endpoint in each respective cohort: change from baseline in HbA1c at Week 32 for Cohort 1 (T2DM) and percent change from baseline in body weight at Week 32 for Cohort 2 (Obesity).

The null hypothesis is that there is no difference between PF-07081532 and placebo on the primary endpoints. The alternative hypothesis is that PF-07081532 is superior (i.e. greater reduction) to placebo on the primary endpoints.

The Type I error rate (α level) used for the statistical inference will be 5% (1-sided). Each dose of PF-07081532 will be tested separately compared to placebo.

No adjustment for multiple comparisons will be made.

5.2. General Methods

The efficacy analyses will be based on the appropriate population for analysis (see Section 4). Analysis using the Evaluable set is aligned with the objectives and endpoints of this study.

In this study, the Cohort 1 (T2DM) and Cohort 2 (Obesity) are defined as administrative strata and will not be adjusted for in statistical analyses. Unless expressly stated, all analyses will be performed for each cohort separately. Randomization was also stratified by gender (Male, Female) which will be included in statistical models. Since this study is exploratory in nature, no multiplicity adjustment of endpoints nor adjustments for multiple comparisons to placebo will be made.

Additional details regarding data derivation statistical methods will be included in the ARP or in amendment to this SAP.

5.2.1. Analyses for Binary Endpoints

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

5.2.2. Analyses for Continuous Endpoints

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

MMRM analyses will be used. The MMRM will include treatment, strata, time, baseline*time and treatment*time as fixed effects, and baseline as a covariate with time fitted as a repeated effect and participant as a random effect. An unstructured correlation matrix will be used, and the Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. In the case where an unstructured correlation matrix cannot converge, a first order autoregressive matrix will be attempted, followed by a compound symmetry correlation matrix. The MMRM model will be fitted to change from baseline to each planned study visit that is estimable. Planned study visits are Weeks 4, 8, 12, 16, 20, 24, 28, and 32. Due to scarcity of data at later visits at the time of study termination, MMRM analyses will be limited to Week 16 for Cohort 1 (T2DM) and Week 20 for Cohort 2 (Obesity). Missing values up to Week 16 for Cohort 1 (T2DM) and up to Week 20 for Cohort 2 (obesity) will be imputed as part of the MMRM model assumptions.

5.2.3. Analyses for Time-to-Event Endpoints

Time-to-event endpoints will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of participants at risk over time. The median, quartiles, and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method. Confidence intervals for medians and quartiles are based on the Brookmeyer-Crowley method.

Confidence intervals for the estimated probability of an event at a particular time point will be generated using the Greenwood formula.

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.

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. Both the absolute change and percent change from baseline in body weight will be calculated. If all duplicate values are missing, body weight will not be imputed and will be set to missing.

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

6. ANALYSES AND SUMMARIES

Scarcity of data at later visits limits some analysis and interpretation of study data. All available safety and efficacy data CCI will be summarized. Statistical models of efficacy data will be limited to Week 16 for Cohort 1 (T2DM) and Week 20 for Cohort 2 (Obesity).

Tabular displays will be ordered with placebo as the left most column, followed by ascending total maintenance dose of PF-07081532 and Rybelsus® as the right most column.

6.1. Primary Endpoint(s)

- Placebo-adjusted change from Baseline in HbA1c at Week 32 for Cohort 1 (T2DM)
- Placebo-adjusted percent change from baseline in and Body Weight at Week 32 for Cohort 2 (Obesity)

6.1.1. Main Analysis

- Estimand strategy: On Treatment (Section 2.2.1)
- Analysis Set: Evaluable (Section 4).
- Analysis methodology: MMRM (Section 5.2.2)
- Intercurrent Events and Missing Data: As per estimands (Section 2.2.1)
- Absolute values and change from baseline will be summarized descriptively by treatment and time point as described in Section 5.2.2. 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

- MMRM for the Evaluable set for Cohort 1 (T2DM) through Week 16 and Cohort 2 (Obesity) through Week 20

6.1.2. Figures

Profile plots of the LS Means (including 90% confidence intervals) over time, with a separate line for each treatment.

6.2. Secondary Endpoint(s)

6.2.1. Binary Secondary Endpoints

The following secondary endpoints are binary categories derived from observed continuous measurements:

- Proportion of Participants who Achieve HbA1c <7% (<53 mmol/mol) at Week 32 for Cohort 1 (T2DM)

- Proportion of Participants who Achieve ≥5%, ≥10%, and ≥15% **body weight loss** at Week 32 relative to Baseline for Cohort 2 (Obesity)

6.2.1.1. Main Analysis

These endpoints will not be summarized but will be derived and included in ADaM datasets.

6.2.2. Continuous Secondary Endpoints

The secondary endpoint of placebo-adjusted, percent change from baseline in **body weight** (kg) at Week 32 in Cohort 1 (T2DM) will be analyzed as described for the primary continuous endpoints.

The following secondary endpoints are continuous and will summarized as described in Section 5.2.2, and no modeling will be performed:

- Placebo-adjusted, change from baseline in **FPG** (mg/dL, mmol/L) at Week 32 in Cohort 1 (T2DM)

- Placebo-adjusted, change from baseline in **HbA1C** (%) in the Rybelsus arm at Week 32 in Cohort 1 (T2DM)

- Placebo-adjusted, **absolute** change from baseline in **waist circumference (cm)** at Week 32 in Cohort 2 (Obesity)

- Placebo-adjusted, **absolute** change from baseline in **waist-to-hip ratio** at Week 32 in Cohort 2 (Obesity)

- Placebo-adjusted, change from baseline in **HOMA-IR** at Week 32 in Cohort 2 (Obesity)

- Placebo-adjusted, change from baseline in **HOMA-S** at Week 32 in Cohort 2 (Obesity)

6.2.2.1. Main Analysis

- Estimand strategy: On Treatment (Section 2.2.1)
- Analysis Set: Evaluable (Section 4).
- Analysis methodology: MMRM (Section 5.2.2) for percent change from baseline in **body weight** (kg) at Week 32 in Cohort 1 (T2DM) only
- Intercurrent Events and Missing Data: As per estimands (Section 2.2.1)
- Absolute values and change from baseline will be summarized descriptively by treatment and time point as described in Section 5.2.2. 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
- MMRM for the Evaluable set for percent change from baseline in body weight (kg) in Cohort 1 (T2DM) through Week 16

6.2.2.2. Figures

Profile plots of the LS Means (including 90% confidence intervals) over time, with a separate line for each treatment.

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6.4. Pharmacokinetic Endpoints

PK data may be used for population PK and/or PK/PD analyses. The objective of such analyses, if conducted, would aim to explore the relationship between concentrations of PF-07081532 or Rybelsus and effect on endpoints of interest and also identification of potential demographic determinants (eg, age, sex, and weight) influencing the observed PK and/or PD. These analyses if conducted, will be reported separately from the main CSR.

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6.6. Subset Analyses

Subset analyses added for other efficacy and/or safety endpoints if required for the CSR would be included as part of an update to this SAP with an amendment prior to database lock or documented in the CSR under changes to planned analysis.

6.7. Baseline and Other Summaries and Analyses

6.7.1. Baseline Summaries

A baseline table (or separate tables, as required) summarizing the following will be produced for Cohort 1 (T2DM) and Cohort 2 (Obesity) separately by treatment and overall: age; gender; race; ethnicity; height; weight; body mass index; waist circumference; waist-to-hip ratio; duration of T2DM; stratification factor; country; HbA1c; FPG; SBP; DBP; as well as duration of metformin for Cohort 1 (T2DM).

6.7.2. Concomitant Medications and Nondrug Treatments

All prior and concomitant medication(s) by incident transaminitis and overall will be reported as described in Section 5.2.1.

Baseline concomitant metformin dose categories (≤500 mg, >500 mg - ≤1000 mg, >1000 mg) will be reported as described in Section 5.2.1.

A separate table listing the use of rescue medication will be produced. The use of rescue medication (grouped by class of medication) will be summarized descriptively by treatment and overall as described in Section 5.2.1. The classes will be defined based on medications used in the study.

6.7.3. Treatment Compliance

A summary table of treatment compliance (by treatment and overall) will be produced according to Section 5.2.2.

6.7.4. Discontinuations

Participant discontinuations and temporary discontinuations from study and from treatment due to AEs will be detailed and summarized by treatment and overall as described in Section 5.2.1.

6.8. Safety Summaries and Analyses

Safety analyses will be performed using the safety analysis set (Section 4). All summaries will be performed separately by cohort.

6.8.1. Adverse Events

An AE is considered TEAE relative to a given treatment if the event starts during the effective duration of treatment (i.e. starting on or after the first dose but before the last dose plus lag time).

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time, whether this occurs during a break in treatment or at the end of treatment, is

attributed to the corresponding treatment period. The lag time is defined by the Pfizer Standard of 365 days post last dose of study intervention.

AEs occurring during the placebo run-in period (i.e., starting from Day -14, inclusive, up to and before the first dose of active treatment on Day 1) will be considered non-treatment emergent.

AEs will be summarized by treatment and overall and in accordance with sponsor reporting.

Incidence and severity of TEAE tables will be summarized by SOC and PT, by treatment and overall. Incidence and severity of TEAE in ≥2% of participants will be summarized by PT, by treatment and overall. In addition, incidence and severity of TEAE tables will be produced by PT by dosing regimen as well as by titration step.

TEAEs, related TEAEs, and SAEs will be reported by PT. The subset of TEAEs occurring in at least 2% of participants will be shown in a separate table.

The prevalence of TEAEs of each nausea, vomiting, and diarrhea will be shown in separate figures. Recurrence of these TEAEs, defined as an observed TEAE that has ended and then a new instance of the same TEAE occurs, will be summarized.

The timing and duration of TEAEs of PTs in GI SOC that are ≥5% in the Rybelsus® label will be plotted per TEAE per participant. The figure for each included PT will display each participant on the y-axis and a line connecting the study days of the start and end date of the TEAE.

Additional AE summaries will include those listed below:

- Events of hypoglycemia
- TEAEs (and SAEs) leading to temporary discontinuation of treatment
- TEAEs (and SAEs) leading to permanent discontinuation and withdrawal of treatment and of study
- Cumulative discontinuation from treatment over time displayed in a figure

6.8.2. Laboratory Data

Laboratory data will be listed and summarized as outlined in Sections 5.2.1 and 5.2.2.

Spaghetti plots will be shown for each of the following separately by cohort and treatment, observations expressed as a function of the upper limit of normal:

- Individual ALT Versus Time
- Individual AST Versus Time
- Individual Alkaline Phosphatase Versus Time

- Individual Total Bilirubin Versus Time
- Individual Direct Bilirubin Versus Time
- Individual Total Bile Acids Versus time, including both central lab and local lab values as well as scheduled and unplanned observations

eDISH plots of Maximum ALT or AST Versus Total Bilirubin will be shown.

6.8.3. Vital Signs

Absolute values and changes from baseline in seated SBP and DBP and pulse rate will be summarized by treatment and time point, as described in Section 5.2.2. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

Maximum absolute values and maximum changes from baseline for vital signs, over all measurements taken post dose will also be tabulated by treatment using categories as defined below. 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 seated SBP and DBP, and maximum increase from baseline for seated pulse rate will be summarized by treatment, as described in Section 5.2.2.

Table 5. Vital Signs Change from Baseline

Parameter	Flag Level	Conventional Units
SBP (seated) I	< 90, >200	mm Hg
DBP (seated)	< 40, >100	mm Hg
Pulse rate (seated)	<40	Bpm
	> 110	Bpm

6.8.4. Electrocardiograms

Changes from baseline for the ECG parameters HR, QT, QTcF, PR interval, and QRS complex will be summarized by treatment and time as described in Section 5.2.2. The frequency of uncorrected QT values above 500 ms will be tabulated. The number (%) of participants with maximum post dose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment as described in Section 5.2.1.

A listing of all ECG results as well as a listing subset to those with abnormal findings will be produced.

Table 6. Safety QTcF Assessment

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

Note: For purposes of reporting study-level results, QTcF interval will be derived using Fridericia's heart rate correction formula applied to databased QT interval, and RR interval.

Table 7. Categories for PR and QRS

ECG Parameter	Increase Categories	Decrease Categories
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	

7. INTERIM ANALYSES

Interim analyses and summaries are provided in the IRC Charter.

8. APPENDICES

Appendix 1. Data Derivation Details

C-SSRS Mapped to C-CASA - Suicidal Ideation and Behavior 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[1]	"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?"

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Appendix 2. List of Abbreviations

Abbreviation	Term
ADaM	analysis data model
AE	adverse event
ALT	alanine aminotransferase
ARP	analysis & reporting plan
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
Bpm	beats per minute
C-CASA	Columbia classification algorithm for suicide assessment
C_{avg}	average concentration
cm	centimeter
CSR	clinical study report
C-SSRS	Columbia suicide severity rating scale
CYP3A	cytochrome P450 3A
DBP	diastolic blood pressure
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FPG	fasting plasma glucose
FPI	fasting plasma insulin
GI	gastro intestinal
HbA1C	glycated hemoglobin
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	homeostatic model assessment for insulin resistence
HOMA-S	homeostatic model assessment for insulin sensitivity
HR	heart rate
hs-CRP	high-sensitivity C-reactive protein
ICD	informed consent document
IRC	internal review committee
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kg	kilogram
LDL-C	low-density lipoprotein
LLQ	lower limit of quantitation
LS	least-squares
MAR	missing at random
mg/dL	milligram per deciliter
mIU/L	
mm Hg	millimeters of mercury
mmol/L	millimoles per liter
mmol/mol	millimoles per mole

Abbreviation	Term
MMRM	mixed-effects model with repeated measures
ms	milliseconds
N/A	not applicable
Ng/L	nanograms per liter
PCD	primary completion date
CCI	
PD	pharmacodynamic(s)
CCI	
PK	pharmacokinetic(s)
CCI	
CCI	
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
CCI	
SOA	schedule of activities
SOC	system organ class
T2DM	Type 2 diabetes mellitus
TEAE	treatment emergent adverse event
TG	triglyceride
U/L	units per liter
ULN	upper limit of normal

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