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

Investigational Product Number:	PF-06882961
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C3421008
Phase:	2a

Short Title: A 12-Week Titration Study to Evaluate Safety, Tolerability, and Pharmacodynamics of PF-06882961 in Adults with Type 2 Diabetes Mellitus and in Non-Diabetic Adults with Obesity

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 2	23 Sep 2020	Title page: Updates made to reflect addition of non-diabetic adults with obesity. Rationale: This study population has been updated with Amendment 2. Section 1.2, Schema: updated to indicate that participant-provided metformin is in participants with T2DM. Rationale: Requirement for background metformin use is only applicable to T2DM participants. Section 1.3, Schedule of Activities: footnote "b" added to table to indicate that regular fingersticks are not required in participants with obesity without T2DM but the glucometer and supplies should be dispensed as a backup in case they have signs or symptoms of hypoglycemia. Added mental health questionnaires (C-SSRS and PHQ-9) due to inclusion of participants with obesity. Rationale: Safety monitoring approach has been updated due to addition of non-diabetic participants with obesity. Section 2, Introduction: updated to indicate that clinical development in obesity is also planned. Rationale: Update provides context for updated study population. Section 2.1, Study Rationale: updated to reflect inclusion and rationale for participants with obesity and without T2DM, in addition to the addition of the higher target dose of 200 mg BID in 2 study arms. Rationale: Updates provide rationale for updated study population and higher dose in 2 study arms. Section 2.2.1, Nonclinical Safety: updated to include

		exposure margins to the updated highest planned dose in this study of PF-06882961 200 mg BID. Rationale: Updates align with higher dose in 2 study arms. Section 2.2.2.2, Clinical Pharmacokinetics: updated to provide additional PK exposure information in participants without T2DM compared with participants with T2DM. Rationale: Updates align with updated study population. Section 3, Objectives and Endpoints: updated to reflect inclusion of participants with obesity and without T2DM. Rationale: Updates align with updated study population. Section 4.1, Overall Design and Figure 1: updated to reflect the following changes: 1. inclusion and rationale for participants with obesity and without T2DM; 2. Addition of Arm 5 (target dose of PF-06882961 200 mg BID) which will be administered to participants with T2DM and participants with obesity and without T2DM; 3. Increase in sample size for placebo arm and total study population. Rationale: Updates provide rationale for updated study population and sample size, addition of 2 study arms and higher dose in 2 study arms. Section 4.2, Scientific Rationale for Study Design and Section 4.3, Justification for Dose: updated to include rationale for inclusion of participants with obesity and without T2DM and rationale for addition of Arms 6 and 7 with target dose of PF-06882961 200 mg BID. Rationale: Updates align with updated study population and higher dose in 2 study arms. Section 5.1, Inclusion Criteria: updated to specify

		inclusion criteria for all participants, criteria for participants with T2DM only and criteria for participants with obesity without T2DM. Also, minimum BMI for participants with T2DM has been increased to 27 kg/m^2 (with no upper limit for BMI), to provide a closer range to participants with obesity without T2DM. Rationale: Updates align with updated study population. Section 5.2.2. Exclusion Criteria All Participants: Added criteria numbers – 12. History of major depressive disorder or history of other severe psychiatric disorders (eg, schizophrenia or bipolar disorder) within the last 2 years; and criteria number 13. Any lifetime history of a suicide attempt. 17. A PHQ 9 score ≥15 obtained at V1, V2 or V3. 18.→ Response of "yes" to question 4 or 5, or on any behavioral question on the C-SSRS at V1, V2 or V3. These updates have been made based on the potential risk related to the product labeling for the injectable GLP-1R agonist liraglutide for obesity. Rationale: Updates align with updated study population. Section 5.3.1, Dietary Restrictions: updated to separate dietary guidelines for participants with and without T2DM. Rationale: Updates align with updated study population. Sections 6.1.1, Administration and 6.3.1 Allocation to Investigational Product: updated to indicate that with addition of Arm 6 and 7, Week 9 will also require 4 tablets BID to maintain the double blind across treatment arms. Table 2 was also updated to include titration scheme for Arm 6 and 7. Rationale: Updates align with titration schemes required for the higher dose in the 2 additional study arms. Section 6.6, Dose Modification: wording updated to

		clarify that scheduled dose titration is used in active dosing regimens. Rationale: Update clarifies that while doses are titrated over the study duration in the active arms, modification of the blinded dosing regimen is not permitted per protocol. Section 8.2.4.1, Home Glucose Monitoring: updated to indicate that regular fingersticks are not required in participants with obesity without T2DM unless they have signs or symptoms of hypoglycemia. Rationale: Updates align with updated study population. Section 8.2.7, Mental Health Questionnaires and associated sub-sections have been added under Safety Assessments. Related sub-sections include: 8.2.7.1, Columbia Suicide Severity Rating Scale (C-SSRS), 8.2.7.1.1, Rater Qualifications, 8.2.7.2, Patient Health Questionnaire – 9 (PHQ-9) and 8.2.7.3, Referral to a Mental Health Professional. Rationale: Updates to safety monitoring align with updated study population. Section 9.1.1, Estimands, Section 9.3, Populations for Analysis and Section 9.4.1 Pharmacodynamic Analyses, updated wording. Rationale: Updates clarify estimands and analyses pertaining to participants with T2DM and those pertaining to participants with obesity without T2DM. Section 9.2, Sample Size Determination, increase in sample size for placebo arm and total study population. Rationales: Updates reflect the changes in the study design.
Amendment 1	08 June 2020	Title page: EudraCT number in the original protocol was not correct and has been updated to Not Applicable, as this study will take place in the United States only.

		Section 1.3. (Schedule of Activities), 8.7.2 (Banked biospecimens) and 8.8.2 (Biomarkers) change have been revised to incorporate Protocol Administrative Clarification Letter (dated 08 Oct 2019) to update the types of Biobank Samples collected. Section 1.3, (Schedule of Activities) has been updated to add collection of banked biospecimens Prep B1.5 and B2.5 at the early termination visit. Rationale: Collection of banked biospecimens at the early termination visit to allow for additional research in cases of early termination if applicable. Section 2.2.1, Nonclinical Safety has been added to provide the most recent toxicology information. This section also includes the embryo-fetal toxicology data, which was previously in Section 4.2. Rationale: Updates align with recently updated Investigator Brochure and all of the toxicology data are presented in the same section. Sections 2.2.2 (Clinical Overview), 2.2.2.1 (Clinical Safety) and 2.2.2.2 (Clinical Pharmacokinetics) have been updated to reflect the completed C3421002 study. Rationale: Updates align with the most recent clinical safety and pharmacokinetics information. Section 4.2 and Appendix 8 (Prohibited Prior/Concomitant Medication) have been revised to list the exclusion of sulfasalazine, simplification regarding the use of potent CYP3A4 inhibitors and extension of timeframe prohibiting use of weight loss drugs. Rationale: CCI [redacted] Weight loss drug extension is to align with liraglutide restriction for glycemic control. Section 4.3, Justification for Dose has been revised to reflect that study C3421002 has completed and data are no longer preliminary. Rationale: C3421002 was completed after initial

		protocol finalization. Section 5.2, Exclusion Criteria, criterion #15 has been revised to lower the systolic and diastolic blood pressure eligibility criteria. Rationale: The cut off for blood pressure has been lowered to a more conservative level to optimize blood pressure control prior to study entry. Section 5.3.1, Dietary Restrictions has been revised to clarify that fasting is required prior to body weight (also a revision to Section 8.6.1 and Appendix 9) but is not required prior to post dose PK sample collection. Additionally, the requirement to withhold blood pressure and lipid modifying medications prior to site has been removed. Rationale: Aligns with updates to Section 8.6.1 and Appendix 9, as body weight must be obtained under standardized conditions. Clarification that fasting is not required prior to post dose PK sample collection has been included given PF-06882961 is dosed with food. Blood pressure and lipid modifying medications may be taken prior to site visits to ensure blood pressure and lipid management is maintained in participants requiring these medications. Section 6.4, Study Intervention Compliance has been updated to provide an example of how many doses may be missed for the placebo run-in duration, depending on differences in visit windows. Rationale: Clarifies the compliance requirement for eligibility. Section 6.5.4, Antihypertensive Medications has been revised to remove language regarding handling of participants who enter the study with a blood pressure of ≥160/100. Rationale: This language is no longer applicable given the revision to exclusion criterion #15. Section 8.2.2.1, Blood Pressure and Pulse Rate has been revised to allow for manual assessment of BP and PR

		only if an automated instrument is not available and also to clarify that the same arm for BP and PR should be used throughout the study, when possible. Rationale: These revisions are made for clarification. Section 8.3: (1) 8.3.1 Time Period and Frequency for Collection AE and SAE Information has been revised to remove the requirement for medical occurrences that begin before the start of study intervention but after obtaining informed consent to be recorded on the Medical History/Current Medical Conditions section of the CRF; (2) 8.3.1.2 Recording Nonserious AEs and SAEs on the CRF has been updated to reflect current sponsor language. Rationale: This revision aligns with the requirement to collect and record all AEs and SAEs from the time informed consent is provided. It also aligns with current sponsor language regarding the recording of AEs and SAEs on the CRF. Section 9.4.2.1, Electrocardiogram Analyses, has been revised to remove summarization of the number of participants with uncorrected QT values >500 msec. Rationale: Safety analyses and summaries will be based on QTcF intervals, not QT intervals. Section 9.4.3, Other Analyses has been revised to clarify that results from any future analyses from pharmacogenomic or biomarker data from banked biospecimens are not planned to be included in the CSR. Rationale: These results are not routinely included in CSRs. Protocol Appendix 4, Section 10.4.2, Female Participant Reproductive Inclusion Criteria the requirement of females to not donate eggs has been removed. Rationale: This revision is made as PF-06882961 does not have risk of genotoxicity; as such the requirement of females to not donate eggs has been removed.
Original	27 September	N/A

protocol	2019	

This amendment incorporates all revisions to date, including Protocol Administrative Clarification letters (PACLs), and amendments made at the request of country health authorities and IRBs/ECs.

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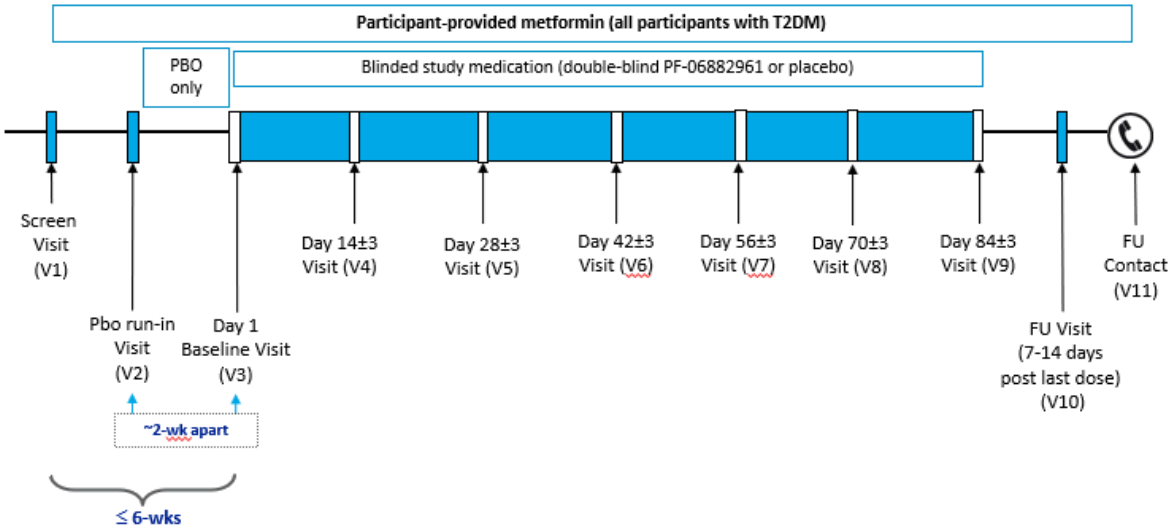
1. PROTOCOL SUMMARY

1.1. Synopsis

Not Applicable (N/A).

1.2. Schema



1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES Section 8 of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, to conduct evaluations or assessments required to protect the well-being of the participant.

Protocol Phase (for abbreviations refer to Appendix 10)	**Screen**	**Run-in**	**Treatment Phase**							**Follow-Up**		**Early Term**
Weeks Relative to Dosing on Day 1	**-6 to -3**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**13-14**	**16-17**	**ET**
Days Relative to Dosing on Day 1	**-42 to -15**	**-14±3**	**1**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**91-98**	**112-119[a]**	**--**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**ET**
Informed consent & demography	x											
Review of eligibility criteria	x	x	x									
Open-ended inquiry for adverse events	x	→	→	→	→	→	→	→	→	→	x	x
Medical history (update only at V2 and V3)	x	x	x									
Review prior or concomitant treatments	x	x	x	x	x	x	x	x	x	x	x	x
Review drug, alcohol/tobacco use	x	x	x	x	x	x	x	x	x	x	x	x
Review contraception use (females only)	x	x	x	x	x	x	x	x	x	x	x	x
Counseling on diet/exercise guidelines		x										
Dispense glucometer, supplies, diary, and provide training		x										
Review drug diary, glucometer & glucose log[b]			x	x	x	x	x	x	x	x		x
Glucose measurement (fasting, via glucometer, on site)		x	x	x	x	x	x	x	x	x		
Mental health questionnaires (C-SSRS, PHQ-9)	x	x	x	x	x	x	x	x	x	x		x
Physical examination (height at Screen only)[c]	x		x						x	x[c]		x
Body weight (in duplicate)	x	x	x	x	x	x	x	x	x	x		x
Supine vital signs assessment	x[d]	x	x[d]	x	x	x[d]	x	x	x[d]	x		x
Supine 12-lead ECG	x		x[d]	x	x	x[d]	x	x	x[d]	x		x
Registration in trial (via IRT)	x											
Randomization in trial (via IRT)			x									
Dispensation of IRT		x[e]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]				
Witnessed dosing on site of IP (AM dose) – with food		x	x	x	x	x	x	x	x			
Compliance via pill count *on site* of ***returned*** IP			x	x	x	x	x	x	x			x
Blood Sampling for:												
-Fasting plasma glucose and HbA1c	x	x	x	x	x	x	x	x	x	x		x
-Hematology, chemistry (including eGFR)	x		x	x	x	x	x	x	x	x		x

Protocol Phase (for abbreviations refer to Appendix 10)	Screen	Run-in	Treatment Phase							Follow-Up		Early Term
Weeks Relative to Dosing on Day 1	**-6 to -3**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**13-14**	**16-17**	**ET**
Days Relative to Dosing on Day 1	**-42 to -15**	**-14±3**	**1**	**14±3**	**28±3**	**42±3**	**56±3**	**70±3**	**84±3**	**91-98**	**112-119[a]**	**--**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**ET**
-FSH (females only), C-peptide	x											
-Pregnancy test (females only)	x	x	x	x	x	x	x	x	x	x		x
Lipids, TSH, free T4, calcitonin, amylase, lipase, TBA, PT/INR/aPTT	x		x		x		x		x	x		x
-PF-06882961 PK (pre-dose unless noted)			x[g]	x	x	x[g]	x	x	x[g]			x
-Banked biospecimen: Prep B1.5 & B2.5			x			x			x			x
-Banked biospecimen: Prep D1 (only Day 1)[h]			x									
Urine Sampling for:												
-Urine drug test	x											
Urinalysis (and microscopy, reflexive)	x		x			x			x	x		x
-On-site urine pregnancy test (females only)[i]	x	x	x	x	x	x	x	x	x	x		x

a. May be a telephone contact, or a visit to the clinic if deemed necessary by the investigator.

b. For participants with obesity only, the review of the glucometer and glucose log should be completed if participants have signs or symptoms of hypoglycemia. Otherwise, regular glucometer monitoring at home is not required.

c. Full physical examination performed according to the SoA. A limited physical examination is performed at the follow-up visit and may be performed at non-specified visits if there are findings during the previous exam or new/open AEs, if appropriate and at investigator discretion.

d. Triplicate assessments (see Section 8.2.2) will be measured at screening, and pre- and post-dose times at Visit 3, Visit 6 and Visit 9, when both pre-dose and post-dose PK measurements are obtained.

e. On V2 only, IP reflects single-blind placebo; it is dispensed via IRT.

f. For V3 through V8, IP is dispensed via IRT and reflects double-blind randomized PF-06882961 or placebo.

g. PK samples collected pre-dose and within the window approximately 2-6 hours post dose.

h. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

i. For V3 through V9, the test result must be reviewed and deemed acceptable (ie, negative), to continue participation in the study.

2. INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake.[1] GLP-1 activation of the GLP-1 receptor (GLP-1R) stimulates insulin release, inhibits glucagon secretion in a glucose-dependent manner, and delays gastric emptying.[2,3] In addition, GLP-1 has been shown to increase satiety and suppress food intake.[4] PF-06882961 is an orally administered, small molecule GLP-1R agonist that has been demonstrated, in nonclinical models, to stimulate glucose-dependent insulin release and suppress food intake with equivalent efficacy to an injectable peptide GLP-1R agonist approved for the treatment of type 2 diabetes mellitus (T2DM). PF-06882961 is in Phase 2 development for the treatment of adults with T2DM. Investigation of the efficacy, safety, and tolerability of PF-06882961 for weight loss in adults with obesity is also being evaluated.

2.1. Study Rationale

The purpose of this multicenter, Phase 2a, randomized, double-blind, sponsor-open, placebo-controlled, parallel-group study is to assess the tolerability, safety, and pharmacodynamic (PD) data for PF-06882961 in participants with T2DM treated with metformin and in participants with obesity, without T2DM. Five different titration schemes of PF-06882961, including one titration scheme to the target dose of 200 mg BID, will be investigated in participants with T2DM, who comprise a majority of the study population. One titration scheme of PF-06882961 to the target dose of 200 mg BID will be investigated in participants with obesity, without T2DM. Differences in tolerability, safety and pharmacokinetics will be explored between participants with T2DM and participants without T2DM, supporting the clinical development of both T2DM and of obesity.

2.2. Background

The increase in the global prevalence of T2DM is largely attributed to rising rates of excess body weight and obesity.[5] T2DM is estimated to affect more than 424 million people worldwide,[6] and the prevalence of T2DM within the United States (US) is estimated to range from 12 to 14%.[7] T2DM is characterized by insulin resistance, a disorder in which cells do not respond effectively to insulin, resulting in higher blood glucose levels. Elevated blood glucose levels and increasing severity of insulin resistance result in the need for more insulin over time, eventually resulting in progressive pancreatic β-cell failure.[8] Patients with poorly controlled T2DM have an increased risk of developing complications associated with both microvascular and macrovascular disease, including nephropathy, neuropathy, retinopathy, cardiovascular disease and stroke; and are at 2 to 4 times increased risk of mortality than adults who do not have diabetes.[9] While existing pharmacological options for the treatment of diabetes may provide satisfactory glycemic control for some patients, there remains a large number of patients who do not achieve target glycated hemoglobin (HbA1c) levels, suggesting a need for additional therapeutic options.

Marketed injectable GLP-1R agonists have demonstrated robust glycemic efficacy, weight loss, and cardiovascular safety, with some agents demonstrating cardiovascular benefit.[10] Based on the clinical history of injectable GLP-1R agonists, an oral GLP-1R agonist is expected to improve glucose control and reduce HbA1c levels in patients with T2DM, while decreasing food intake and body weight and avoiding the subcutaneous injection required by currently available peptidic GLP-1R agonists.

2.2.1. Nonclinical Safety

General toxicology studies have been completed in cynomolgus monkeys up to 6 months in duration (with a 3-week lead-in and 1-month recovery) and in rats up to 6 months in duration (with a 1-month recovery). The exposure limits for plasma concentrations of PF-06882961 for clinical studies are based on the exposure at the no observed adverse effect level (NOAEL) dose of 250 mg/kg/day in the 6-month with 1-month recovery toxicology study in rats, CCI [redacted] In the 6-month toxicity study in rats with 1-month recovery, the NOAEL was 250 mg/kg/day CCI [redacted] The exposure margins at 250 mg/kg/day were 27-fold (C_{max}, free) and 14-fold (AUC_{24}, free), to the predicted human exposures at the highest projected mean exposure of PF-06882961 in this study (200 mg BID in T2DM participants).

CCI [redacted]

At the NOAEL dose of 150 mg/kg/day in the 13-week study with 3-week lead-in, exposure margins were 6.2- and 4.5-fold for C_{max} (free) in males and females, respectively, and were 5.1- and 4.7-fold for AUC_{24} (free) in males and females, respectively, at the highest projected mean exposure of PF-06882961 in this study (200 mg BID in T2DM participants).

Embryo-fetal developmental studies were completed in rats and rabbits. Based on the lack of maternal toxicity or adverse effects on embryo-fetal development, the NOAEL for maternal and developmental toxicity in rats was 500 mg/kg/day (highest dose evaluated). CCI [redacted]

In embryo-fetal studies conducted in rabbits, the NOAEL for maternal and developmental toxicity was 250 mg/kg/day. CCI [redacted]

PF-06882961 was negative in genetic toxicity testing and photosafety endpoints. A risk assessment of the target organ toxicities noted in the repeat-dose toxicity studies is provided in the Investigator Brochure (IB).

Refer to the IB for more details on the nonclinical safety of PF-06882961.

2.2.2. Clinical Overview

To date, 3 clinical studies, C3421001, C3421002 and C3421003 have been completed with PF-06882961. In C3421001 and C3421003, healthy participants were randomized to receive single oral doses of PF-06882961 (or matching placebo). In C3421002, adult participants with T2DM were randomized to receive oral doses of PF-06882961 (or matching placebo) for 28 days, and safety results from this study are provided in Section 2.2.2.1. Refer to the investigator's brochure (IB) for more details on these studies and the known drug class effects on marketed injectable GLP-1R agonists.

2.2.2.1. Clinical Safety

Clinical data from the completed C3421001, C3421002 and C3421003 studies are provided in the IB for PF-06882961.

In the C3421002 study, PF-06882961 doses ranging from 10 mg BID to 120 mg BID were generally safe and well tolerated. A total of 98 participants with T2DM on a background of metformin were randomized to receive PF-06882961 or matching placebo in a 3:1 randomization ratio for 28 days, and 92 participants completed the study. Six (6) participants discontinued from the study, of which 2 withdrew from the study due to adverse events and 4 withdrew during the treatment or follow up period for non-treatment related reasons.

A total of 319 all-causality treatment-emergent adverse events (TEAEs) were reported in these participants, of which a majority (294 or 92%) were mild in intensity, 23 (or 7%) were moderate, and 2 (or 1%) were severe in intensity. A summary of adverse events (AEs) by randomized treatment is presented in the table below.

Table 1. Summary of Treatment-Emergent Adverse Events in C3421002

	Placebo	PF-06882961 Dose[a]							
		10 mg BID	15 mg BID[b]	50 mg BID[b]	70 mg BID	120 mg BID	120 mg BID ST	120 mg QD	200 mg CR QD
Number of participants evaluable for TEAEs	25	9	9	10	9	9	9	8	10
Number of Participants with TEAEs	17	6	8	10	8	8	9	8	9
Number of Adverse Events	44	8	16	45	31	43	50	35	47

ST= slow titration; CR= controlled release formulation; BID = twice daily; QD = daily.

a. PF-06882961 dose reflects the randomized target dose for the group. Note that some participants in the 50 mg BID, 120 mg BID and 120 mg BID ST groups include subject(s) that, due to tolerability, did not remain on the target dose.

b. Neither the PF-06882961 15 mg BID nor the 50 mg BID dose groups received titration.

The most frequently reported TEAEs were nausea (49.0%), dyspepsia (32.7%), vomiting (26.5%), diarrhea (24.5%), headache (23.5%), and constipation (20.4%). In addition, there was 1 symptomatic hypoglycemic adverse event (AE) that was reported in 1 subject in the 120 mg BID group. This AE was non-fasting, mild in severity and of limited duration.

No deaths occurred in the C3421002 study. Two (2) participants experienced 2 severe TEAEs during the study, 1 of which occurred in the dosing period and was considered treatment related, and the other occurred during the follow-up period and was not considered treatment related. The latter participant experienced 2 non-treatment-related serious adverse events (SAEs), 1 of which occurred in the follow-up period and was a TEAE of severe intensity, and the other SAE occurred outside of the study reporting period.

While there were isolated values for laboratory tests, vital signs and electrocardiogram (ECG) intervals outside of the reference ranges, no clear adverse trends were apparent in these parameters. As has been reported for marketed GLP-1R agonists,[10,11] increases in heart rate have been observed, with mean increases ranging from 5 to 15 beats per minute (bpm) across doses administered to date, and most heart rate values within the normal range.

2.2.2.2. Clinical Pharmacokinetics

The clinical pharmacokinetics (PK) of PF-06882961 in adult participants has been evaluated in three completed studies: C3421001, C3421002, and C3421003. The results of these completed studies are summarized in the PF-06882961 IB.

CCI

[redacted]

2.3. Benefit/Risk Assessment

Based on the clinical history of injectable GLP-1R agonists, an oral GLP-1R agonist is expected to improve glucose control, reduce HbA1c levels, diminish food intake, and decrease body weight in patients with T2DM, while avoiding the requirement for subcutaneous injections that accompanies currently available peptidic GLP-1R agonists.

In line with the clinical profile of marketed GLP-1R agonists,[12,17,18] the most frequently reported AEs with PF-06882961 administration have been nausea, diarrhea, dyspepsia, headache, and vomiting. In addition, as has been reported for marketed GLP-1R agonists, increases in heart rate have been observed with PF-06882961 administration, with most heart rate values within the normal range.

Considering all available clinical and nonclinical data, the benefit-risk profile of PF-06882961 is favorable and supports continued clinical development in patients with T2DM.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06882961 may be found in the IB which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

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). • 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.
• 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.

Objectives	Endpoints	Estimands
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).	

For all endpoints, baseline is defined as the result closest prior to dosing at Visit 3 (Day 1).

4. STUDY DESIGN

4.1. Overall 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.

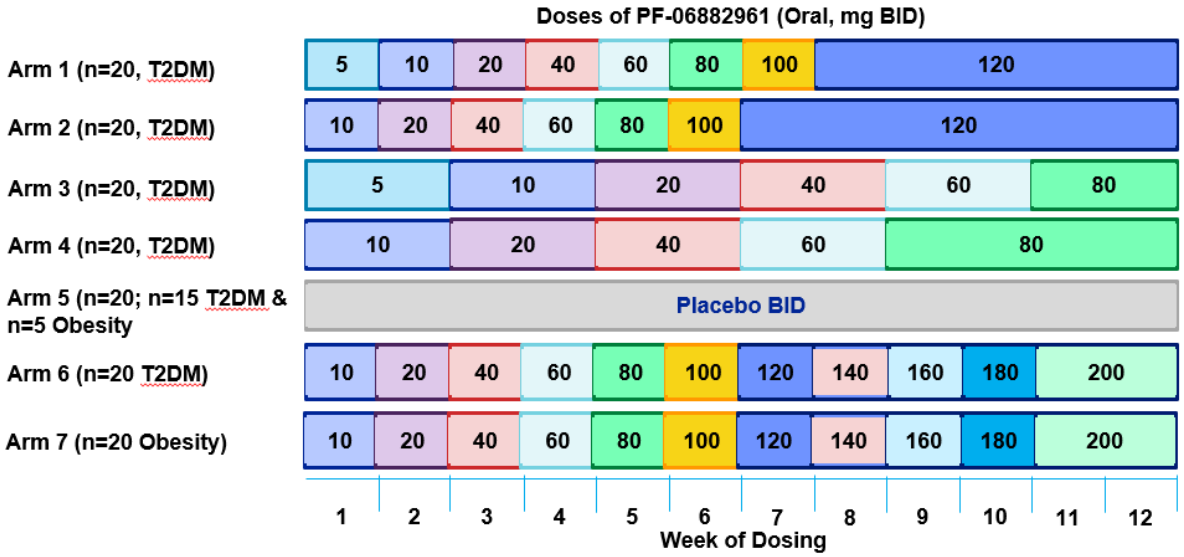
For participants with T2DM, the metformin dose (at least 500 mg/day) must have been stable for at least 60 days prior to the screening visit (Visit 1) and should remain the same until the first follow-up visit (ie, Visit 10, Week 13-14), except in circumstances where a dose change is deemed medically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



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.

4.2. Scientific Rationale for Study Design

This study is designed to assess the tolerability, safety, and PD of PF-06882961 in participants with T2DM and in non-diabetic participants with obesity over 12 weeks of dosing. A single-blind placebo-run-in period (Visit 2 to Visit 3) is included in this study to familiarize participants with the study treatment regimens and to exclude those who are not compliant with blinded placebo dosing prior to randomization. Study intervention compliance is described in Section 6.4. Clinical laboratory tests, assessment of vital signs and 12-lead ECGs, physical examination, and AE monitoring will provide data to evaluate the tolerability, safety, and PD of PF-06882961.

This study will assess tolerability of PF-06882961 at different starting doses (5 mg BID vs 10 mg BID), as well as tolerability of PF-06882961 at different duration of each titration step (1 week vs. 2 weeks), and the tolerability of different target doses (80 mg BID, 120 mg BID and 200 mg BID). The placebo arm is added to facilitate blinding to active treatment and to mitigate bias in reporting of AEs.

CCI [redacted] Therefore, to compare tolerability, safety and PK exposures directly in this study, the study population includes participants with obesity without T2DM, to target a similar BMI range as patients with T2DM and to support clinical development in T2DM and obesity.

Published data from marketed GLP-1R agonists suggests that gastrointestinal (GI) tolerability may be different between men and women, therefore randomization will be stratified based on biological sex.

CCI [redacted]

CCI [redacted]

As part of the clinical safety laboratory tests, calcitonin, amylase, and lipase will be assessed, as these laboratory parameters have been shown to increase with marketed GLP-1R agonists.[12] In addition, thyroid stimulating hormone (TSH), free thyroxine (FT4), lipids, coagulation profile and total bile acids (TBA) will be assessed, based on non-adverse findings in the nonclinical studies with PF-06882961. Assessment of suicidal ideation and behavior by the C-SSRS[19] and PHQ-9[20] will also be performed based on the potential risk related to the product labeling for the injectable GLP1R agonist liraglutide for obesity.[21]

While GLP-1R agonists typically are not associated with hypoglycemia unless co-administered with anti-diabetic agents that can cause hypoglycemia (such as insulin or sulfonylureas), blood glucose concentrations will be monitored throughout the study via glucometer, and monitoring of symptomatic hypoglycemic AEs (HAEs) will be performed.

Body weight will be measured in duplicate at all study visits, except Visit 11, as GLP-1R agonists have been shown to decrease food intake and body weight. The collection of blood samples, specifically fasting plasma glucose (FPG) and HbA1c will assist in the time- and dose-related PD response.

Both females of childbearing potential, as well as those who are of non-childbearing potential, will be enrolled given the availability of embryo fetal developmental (EFD) toxicity studies with PF-06882961. However, as marketed GLP-1R agonists are listed as contraindicated in pregnancy, the use of a highly effective method of contraception is required and measures will be taken to limit the risk of pregnancy in the female population enrolled (see Schedule of Activities and Appendix 4 re: contraception) for additional information regarding contraception use and monitoring.

The potential risk of exposure to PF-06882961 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the no-observed-adverse-effect level (NOAEL) for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[11]

Banked biospecimens will be collected for exploratory pharmacogenomic/genomic/ biomarker analyses and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

4.3. Justification for Dose

The target doses (planned dose at end of study) in the C3421008 study of 80 mg BID (Arms 3 and 4)and 120 mg BID (Arms 1 and 2) represent the 2 top doses being assessed in the Phase 2b dose ranging study in T2DM with PF-06882961. As described in Section 2.2.2.1, more AEs were observed in the 120 mg BID cohort in study C3421002, relative to the 70 mg BID cohort. However, it is not known if tolerability at higher dose levels would be different using titration schemes that take longer than 4 weeks. Based on data from the C3421002 study, the glucose lowering effect of PF-06882961 is expected to be similar to that of marketed GLP-1R agonists. CCI [redacted]

Although doses of >120 mg BID are not anticipated to be needed for glycemic efficacy in T2DM participants, based on experience from marketed GLP-1 agonists, doses needed to maximize weight loss are generally higher than what are needed for glycemic efficacy. For this reason, a higher dose of PF-06882961 is being assessed in this study (200 mg BID, Arm 6) to assess the tolerability of this dose following an extended titration scheme of 10 weeks. The starting dose and titration scheme for Arms 6 and 7 is similar to Arm 2 (Figure 1), but the titration scheme continues at a 1-week interval over a longer duration to achieve a higher target dose. This additional 200 mg BID arm in T2DM may facilitate development of PF-06882961 for treatment of obesity in participants with T2DM.

Although the steady-state exposures of PF-06882961 at 200 mg BID in T2DM participants are expected to be higher than that encountered in previous clinical studies (120 mg BID in C3421002), reasonable tolerability of this dose may be expected based on the extended 12-week titration scheme. Moreover, the predicted exposure at 200 mg BID in participants with obesity and without T2DM is expected to have a 27- and 14-fold margin under the unbound NOAEL for the 6 month rat toxicology study for C_{max} and AUC, respectively (Section 2.2.2.2).

CCI [redacted] Inclusion of a cohort of participants with obesity and not T2DM has been included at the highest dose (200 mg BID) to compare PK, PD and tolerability between the 2 populations.

As the duration in the multiple ascending dose study C3421002 was limited to 4 weeks, the time course of titration in this study was less than 4 weeks. In the current study, the doses will be titrated to the highest doses over a 10-week duration, which is expected to improve the tolerability of PF-06882961, and therefore doses of up to 200 mg BID are viewed as appropriate for assessment in this study.

This study will also assess the appropriate starting dose for titration of PF-06882961. While 10 mg BID of PF-06882961 was generally well tolerated in C3421002, a lower dose of 5 mg BID might be better tolerated than 10 mg BID and improve tolerability of subsequent titration steps.

While this study is designed with target doses of ≥80 mg BID, intermediate doses of 10 to 60 mg will also be assessed in this study, with tolerability of titration schemes leading to these intermediate doses.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the follow-up visit (Visit 11), approximately 28 to 35 days post last dose of double-blind investigator product (IP).

The end of the study is defined as the date of the follow-up last visit (Visit 11) of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

5.1.1. Inclusion Criteria for All Participants

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 75 years, inclusive, at Visit 1 (screening).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures, including the ability to perform self-monitoring blood glucose at a frequency deemed appropriate by the investigator.

Informed Consent:

3. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.1.2. Additional Inclusion Criteria Only for Participants with T2DM

1. Participants with T2DM who are treated with metformin. Metformin dose (at least 500 mg/day) must have been stable for at least 60 days prior to the screening visit (Visit 1).

2. HbA1c ≥7.0% and ≤10.5% at screening (Visit 1) as assessed by the study specific central laboratory. A single repeat is allowed, if deemed necessary.

3. Body mass index (BMI) ≥27 kg/m^2; and a total body weight >50 kg (110 lbs). Body weight must have been stable (<5% change) for at least 90 days prior to screening (Visit 1) as per participant self-report.

5.1.3. Additional Inclusion Criteria Only for Participants with Obesity without T2DM

1. BMI ≥30 kg/m^2; and a total body weight >50 kg (110 lbs). Body weight must have been stable (<5% change) for at least 90 days prior to screening (Visit 1) as per participant self-report.

2. HbA1c <6.5% at screening (Visit 1) as assessed by the study specific central laboratory. A single repeat is allowed, if deemed necessary.

3. FPG <126 mg/dL at screening (Visit 1) as assessed by the study specific central laboratory. A single repeat is allowed, if deemed necessary.

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria for Only Participants with Obesity without T2DM

1. Diagnosis of T2DM.

5.2.2. Exclusion Criteria for All Participants

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or IP administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

2. Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, or any area of intestinal resection, active inflammatory bowel disease or pancreatic insufficiency).

3. Diagnosis of type 1 diabetes mellitus or secondary forms of diabetes.

4. History of myocardial infarction, unstable angina, arterial revascularization, stroke, New York Heart Association Functional Class II-IV heart failure, or transient ischemic attack within 6 months of screening (Visit 1).

5. Any malignancy not considered cured (except basal cell carcinoma and squamous cell carcinoma of the skin); a participant is considered cured if there has been no evidence of cancer recurrence in the previous 5 years.

6. Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2), or participants with suspected MTC per the investigator's judgement.

7. Acute pancreatitis or history of chronic pancreatitis.

8. Symptomatic gallbladder disease.

9. Participants with a known medical history of active proliferative retinopathy and/or macular edema.

10. Participants with a known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C, or primary biliary cirrhosis.

11. Participants with known history of human immunodeficiency virus (HIV).

12. History of major depressive disorder or history of other severe psychiatric disorders (eg, schizophrenia or bipolar disorder) within the last 2 years.

13. Any lifetime history of a suicide attempt.

Prior/Concomitant Therapy:

14. See Appendix 8 for details regarding prohibited prior/concomitant medication.

Prior/Concurrent Clinical Study Experience:

15. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of IP used in this study (whichever is longer).

16. Known prior participation in a trial involving PF-06882961 or known intolerance or hypersensitivity to a GLP-1R agonist.

Diagnostic Assessments:

17. A PHQ-9 score ≥15 obtained at V1, V2 or V3.

18. Response of "yes" to question 4 or 5, or on any behavioral question on the C-SSRS at V1, V2 or V3.

19. Screening (Visit 1) supine blood pressure (BP) ≥160 mm Hg (systolic) or ≥100 mmHg (diastolic), following at least 5 minutes of supine rest. BP should be measured in triplicate and the average of the 3 BP values should be used to determine the participant's eligibility. **Note:** Participants with an arm circumference greater than the largest cuff size or those with a mid-arm circumference >52 cm are not eligible.

20. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline corrected QT interval [QTcF] >450 msec, complete left bundle branch block [LBBB], signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree atrioventricular [AV] block, or serious bradyarrhythmias or tachyarrhythmias).

    - If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility.

21. A positive urine drug test at screening.

    - ***Note:*** Participants who have been prescribed opiates/opioids or benzodiazepine and report the use of these drugs to the investigator at screening (Visit 1) may be allowed to participate with notification to the sponsor.

22. Participants with ANY of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study specific central laboratory and confirmed by a single repeat test, if deemed necessary:

    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level ≥2 x upper limit of normal (ULN).

    - Total bilirubin level ≥1.5 x ULN.

    - Fasting C-peptide <0.8 ng/mL.

    - TSH >1.5 x ULN.

- Serum calcitonin > ULN.
- Amylase or lipase > ULN.
- Fasting plasma glucose >270 mg/dL (15 mmol/L) at screening visit (Visit 1) or single-blind placebo run-in (Visit 2).
- Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[14]

Other Exclusions:

23. Compliance of <89% (based on pill count) during the 2-week run in period, as assessed prior to randomization on Day 1 (Visit 3).

24. History of regular alcohol consumption exceeding 7 drinks/week for female participants or 14 drinks/week for male participants (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before screening (Visit 1).

25. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

26. Unwilling or unable to comply with the criteria in the Lifestyle Considerations Section 5.3 of the protocol.

27. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

5.3.1. Dietary Restrictions

1. Participants must abstain from all food and drink (except water) for at least 8 (preferably 10) hours prior to any body weight and blood sample collection(except post-dose PK samples).

2. IP must be administered BID with food, approximately 10 to 12 hours apart.

3. On scheduled morning visits to the site, from Visit 2 through Visit 9, participants should be instructed to arrive without having morning meal/breakfast, self-administration of IP, *and for participants with T2DM only,* morning dose of metformin for the given day. The above-mentioned medications will be administered with food at the site. Note: Participants may take their morning dose of

antihypertensive and/or lipid modifying medication per their usual routine, if applicable.

4. Participants will be counseled on appropriate dietary and lifestyle guidelines at Visit 2 and asked to maintain these guidelines throughout participation in the study.

    - For participants with T2DM, counseling on dietary guidelines should be in accordance with local medical standards of care for patients with T2DM.

    - For participants with obesity without T2DM, counseling on dietary guidelines should be in accordance with local medical standards of care for patients with obesity.

    - ***Note***: Participation in formal weight loss programs should be avoided during participation in this study.

5.3.2. Alcohol, Caffeine, and Tobacco

- Intake of alcohol is permitted in moderation (refer to exclusion criterion 24 for acceptable amount of alcohol consumption).

- Caffeine containing products will be permitted during the study with the following restrictions: caffeine containing products may not be consumed within 1 hour prior to measuring vital signs and ECGs.

- Use of nicotine-containing products is permitted in this study with the following restrictions: nicotine-containing products may not be used within 1 hour prior to measuring vital signs and ECGs.

5.3.3. Physical Activity

Participants will not be permitted to perform physically strenuous exercise (for example: heavy lifting, weight training, calisthenics and aerobics) within 48 hours prior to blood sample collections; walking at normal pace is permitted.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the female participants have selected an appropriate method of contraception from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected

contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to IP at Visit 3. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

A participant who qualified for this study but did not enroll within the protocol prescribed screening period may be re-screened. All screening procedures must be repeated, and the participant assigned a new 8-digit study-specific subject identification (SSID) number.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term IP may be used synonymously with study intervention. For this study, the IP is PF-06882961 and matching placebo tablets; and will be administered orally, BID, with food.

Treatment phase IP will be packaged in blister cards containing blinded PF-06882961 or matching placebo for oral administration. Treatment assignment will be blinded, and blister cards will be labeled according to local regulatory requirements. For single-blind placebo run-in, tablets will be packaged in blinded-label blister cards according to local regulatory requirements.

Participants will continue taking their own metformin medication at the same total daily dose that was prescribed prior to study entry, except in circumstances where a dose change is deemed medically necessary.

6.1. Study Intervention(s) Administered

Intervention Name	PF-06882961	Placebo for PF-06882961
ARM Name	Active	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	2.5 mg, 10 mg, 40 mg, and 100 mg	0 mg
Dosage Level(s)	Dose amount and frequency – refer to Figure 1	0 mg BID
Route of Administration	Oral	Oral
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IP Manual.	Provided centrally by the sponsor. Refer to the IP Manual
Packaging and Labeling	Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement. Blinded labels will be utilized for blister packs.	Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement. Blinded labels will be utilized for blister packs.

6.1.1. Administration

All doses will be blinded and consist of 3 to 4 tablets administered BID via a blister pack.

Four (4) tablets BID will be administered during the 2-week single-blind placebo run-in and after randomization, during Weeks 1, 2 and 9 of dosing. Three (3) tablets will be administered BID during Weeks 3 to 8 and weeks 10 to 12 of dosing. Single-blinded blister cards will be used for the placebo run-in period. The dosing regimens after randomization will look the same across arms for each dosing window. Blister cards will look the same across all study arms and will contain the same number of tablets for the same time point in treatment.

After randomization during Weeks 1, 2 and 9 of dosing, participants will take 4 tablets of IP (PF-06882961 or matching placebo) in the morning with food and 4 tablets of IP in the evening with food, approximately 10 to 12 hours apart and at approximately the same time each day. Participants will take a total of 8 tablets of IP daily. The same dosing paradigm will be used during the single-blind placebo run-in period.

During Weeks 3 to 8 and Weeks 10 to 12 of dosing, participants will take 3 tablets of IP (in the morning with food and 3 tablets of IP with the evening with food approximately 10 to 12 hours apart and at approximately the same time each day. Participants will take a total of 6 tablets of IP (PF-06882961 or matching placebo) daily.

Participants will swallow the IP whole, and will not manipulate or chew the IP prior to swallowing. To maximize tolerability of PF-06882961 dose will be titrated over a period of 6 to 10 weeks.

The actual titration schemes for PF-06882961 to be used in this study are provided in Table 2 below. The regimen for Arm 5 (the placebo arm) will be placebo tablets administered BID with food in the morning and evening. Arms 1 to 7 are also depicted in Figure 1.

Table 2. Titration Schemes

Week of Study	Arm 1	Arm 2	Arm 3	Arm 4	Arms 6 and 7
1	5 mg BID	10 mg BID	5 mg BID	10 mg BID	10 mg BID
2	10 mg BID	20 mg BID	5 mg BID	10 mg BID	20 mg BID
3	20 mg BID	40 mg BID	10 mg BID	20 mg BID	40 mg BID
4	40 mg BID	60 mg BID	10 mg BID	20 mg BID	60 mg BID
5	60 mg BID	80 mg BID	20 mg BID	40 mg BID	80 mg BID
6	80 mg BID	100 mg BID	20 mg BID	40 mg BID	100 mg BID
7	100 mg BID	120 mg BID	40 mg BID	60 mg BID	120 mg BID
8	120 mg BID	120 mg BID	40 mg BID	60 mg BID	140 mg BID
9	120 mg BID	120 mg BID	60 mg BID	80 mg BID	160 mg BID
10	120 mg BID	120 mg BID	60 mg BID	80 mg BID	180 mg BID
11	120 mg BID	120 mg BID	80 mg BID	80 mg BID	200 mg BID
12	120 mg BID	120 mg BID	80 mg BID	80 mg BID	200 mg BID

Morning dosing will occur with the food at the site at Visit 2 through Visit 9. Participants will be instructed to arrive at the site in the fasted state, bring their IP with them and to delay self-administration of IP and concomitant medications, if appropriate (as described in Section 5.3.1), on scheduled visit days until they arrive for their outpatient clinic visit.

Participants should be instructed that if they forget to take their morning dose at their usual time, they should take the missed dose as soon as possible (with food) on the day it was missed; however, there must be at least an 8-hour interval between the missed dose and the next dose. If a dose is missed and the interval to the next dose is less than 8 hours, the missed dose should not be administered.

Dosing and administration instructions along with the dosing diary, will be provided to participants to support at-home dosing of IP.

If participants schedule a visit prior to the protocol specified visit day they should be instructed by the investigator or site staff to continue dosing from the blister card they were dispensed previously.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an IP accountability form/record. All IP that it taken home by the participant, both used and unused, must be returned to the investigator by the participant.

4. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product (IP) manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

8. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the

study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the investigational product (IP manual).

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

The 2-week single-blind placebo run-in tablets will be dispensed at Visit 1 using an interactive response technology (IRT) drug management system. The same IRT drug management system will be used to dispense the IP from Visit 2 to Visit 8. A qualified staff member will dispense the IP via unique container numbers in the blister cards provided, in quantities appropriate for the study visit schedule. The participant should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

Allocation of participants to treatment groups will proceed through the use of an IRT) system (interactive Web-based response [IWR]).

A randomization code using the method of random permuted blocks will be utilized to randomize eligible participants with T2DM treated with metformin in a 4:4:4:4:4:3 ratio (1 of 5 active dosing regimens of PF-06882961 or placebo) and non-diabetic participants with obesity in a 4:1 ratio (1 active dosing regimen of PF-06882961 or placebo) prior to the first dose of IP.

Participants will be stratified at randomization (Day 1) by population (T2DM vs. non-diabetic) and by biological sex (men vs. women).

The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when IP is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

IP will be dispensed at the study visits summarized in the SoA.

Returned IP must not be re-dispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF).

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

Participant compliance with IP will be assessed at each visit as noted in the SoA. Compliance will be assessed by counting returned tablets. Through Visit 8, which occurs during the first 10 weeks of dosing when participants may be receiving titrated doses as part of their blinded regimen, sites should assess the blister cards for compliance; however, the cards should remain in the possession of the participant. Compliance (as assessed by tablet count) will be defined as self-administration, by the participants, of:

- ≥89% of the study-supplied placebo administered during the single-blind placebo run-in period. Based on the visit window, for a placebo run-in that is 11-13 days, up to 2 missed doses are allowed, and for a placebo run-in that is 14-17 days, up to 3 missed doses are allowed. Participants who do not meet this compliance threshold are not eligible to be randomized into the study (See Section 5.2).

- ≥80% of the study-supplied IP from Day 1 (Visit 3) through Week 12 (Visit 9), inclusive. Investigators must closely follow non-compliant, randomized, participants to enhance their adherence to treatment. Any participant who fails to meet the criterion of ≥80% compliance will be re-educated by the site staff on the importance of compliance with IP.

Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

6.5. Concomitant Therapy

Participants in this study will be allowed to be on certain concomitant medications that have been prescribed. Attempts should be made not to alter the doses and regimens of metformin or any concomitant medications after randomization and for the duration of participation in this study, except in circumstances where a change in dose is deemed medically necessary. Any changes must be captured in the CRF. Additionally, many over-the-counter medications are also permitted during this study.

Treatments taken within 28 days before the first dose of randomized IP on Day 1 will be documented as prior treatment. Treatments taken after the first dose of randomized IP will be documented as concomitant treatment.

All concomitant treatments, both prescription and over-the-counter taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

See Appendix 8 for details regarding prohibited concomitant medications. Sites are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are women of childbearing potential (WOCBP) (see Appendix 4).

6.5.1. Metformin

All participants with T2DM are required to be taking metformin monotherapy prior to inclusion in this study as listed in Section 5.1. Participants must have been taking a stable dose of metformin (≥500 mg/day) for at least 60 days prior to the screening visit (Visit 1). Participants will continue taking their own metformin at the same total daily dose that was prescribed prior to study entry through the first follow-up visit (ie, Visit 10, Week 13-14), except in circumstances where a change in dose is deemed medically necessary. For study visit days, participants should be instructed to refrain from taking morning doses at home and to bring the metformin to the site for dosing at the same time as their blinded IP. For participants taking metformin more than once a day, the timing should be approximately the same on each day.

6.5.2. Medications for Glycemic Control

Aside from metformin, the use of other medications for glycemic control is not permitted in this study unless the participant meets the protocol defined glycemic rescue criteria (see Section 8.2.4.3).

6.5.3. Glycemic Rescue Medicine

Participants with hyperglycemia as defined in Section 8.2.4.3 should be offered glycemic rescue medication as an add on to their randomized treatment.

Glycemic rescue medication should be prescribed according to local label and obtained locally. The following glycemic rescue medications may be used: sulfonylureas, or sodium glucose co-transporter 2 (SGLT2) inhibitors. For participants who were taking a dose of metformin lower than the approved dose, increasing the metformin dose may be instituted as glycemic rescue medication, as long as the dose does not exceed the highest approved dose in the country of participation.

The following medication are NOT permitted as glycemic rescue medications: GLP-1R agonists, DPP-4 inhibitors, amylin analogues, thiazolediediones (TZDs) or insulin.

The date of glycemic rescue medication administration as well as the name and dosage regimen of the glycemic rescue medication must be recorded on the CRF.

Participants receiving glycemic rescue medication should continue to follow all protocol specified visits and procedures according to the SoA.

There is no rescue therapy to reverse the AEs observed with PF-06882961. Standard medical supportive care must be provided to manage the AEs, including administration of carbohydrates to treat HAEs (see Section 8.2.4.2.1).

6.5.4. Antihypertensive Medications

The use of background antihypertensive agent(s) is permitted unless otherwise noted in Appendix 8. Doses of antihypertensive agent(s) must be stable for at least 4 weeks prior to screening and throughout the study, except in circumstances where a change in dose is deemed medically necessary. Any changes in doses of these medications must be captured in the CRF.

6.5.5. Lipid Modifying Medications

The use of background lipid modifying agents is permitted unless otherwise noted in Appendix 8. Doses of lipid modifying agents must be stable for at least 4 weeks prior to screening and throughout the study, except in circumstances where a change in dose is deemed medically necessary. Any changes in doses of these medications must be captured in the CRF.

6.6. Dose Modification

Dose titration schemes are utilized for each study intervention dosing arm in this study as described in Section 6.1.1. However, each dosing regimen will be provided in blister packs, and dose adjustment will not be permitted per protocol.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue IP. If a safety or tolerability concern arises, in particular if not responsive to symptomatic management, dosing with double-blinded IP may be stopped in an individual participant at investigator discretion.

If IP is permanently discontinued, the participant remains in the study and continues to follow all protocol specified visits and procedures according to the SoA.

The site should notify the Sponsor Medical Monitor or Sponsor Clinician if the below criteria for permanent discontinuation are met.

Note that discontinuation of IP does not represent withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Criteria for Discontinuation

Discontinuation of IP must occur for a participant meeting any of the following conditions:

- Criteria for a potential Hy's law case are met (see Appendix 6).
- Intent to become pregnant or pregnancy confirmed by serum beta human chorionic gonadotropin (β-hCG) testing.
- Based on mental health assessment as outlined in Section 8.2.7, should be discontinued from dosing at the discretion of the investigator.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early termination visit should be conducted. See the SoA for assessments to be collected at the time of early termination and follow-up and for any further evaluations that need to be completed.

The early termination visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of IP or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 276 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Physical Examinations

Physical examinations are performed as indicated in the SoA.

Physical examinations may be conducted by a physician, trained physician's assistant or nurse practitioner as acceptable and according to local regulation. A complete physical examination will include, at a minimum, assessments of the head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal and neurological systems.

Height will be measured at screening only.

A limited physical examination is performed at the follow-up visit and may be performed at non-specified visits if there are findings during the previous physical examination or new/open AEs, if appropriate and at investigator discretion. The limited physical examination will be focused on general appearance, lungs, cardiovascular system, and participant reported symptoms.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

8.2.2.1. Blood Pressure and Pulse Rate

In this study, assessment of vital signs (systolic blood pressure (BP), diastolic BP, and pulse rate) will occur at the nominal time points specified in the SoA per the following specifications:

- At screening, the participant's arm circumference should be measured (eg, using a flexible anthropometric tape) at the midpoint of the length of the upper arm and the appropriate cuff selected and used throughout the study.
    - ***Note:*** Participants with arm circumference greater than the largest cuff size available at the site or >52 cm are not eligible.
- BP and pulse rate will be measured via an automated device using an oscillometric method (not auscultation).
    - Assessment of BP and pulse rate can be manual (rather than using an automated device), only if an automated device is not available; however when done manually pulse rate must be measured in the brachial/radial artery for at least 30 seconds.
- Supine BP and pulse rate will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg, following a rest of at least 5 minutes. The assessment at Visit 3 (Day 1) will serve as the participant's baseline. Triplicate assessments will be measured at screening, and pre- and post-dose times at Visit 3, Visit 6 and Visit 9 with a brief interval (eg, 2-4 minutes) between successive triplicate assessments.
- Same arm (preferably the dominant arm) will be used for BP and pulse rate assessments throughout the study, whenever possible.
- Participants should be instructed not to speak during BP and pulse rate measurements.
- See Appendix 9 for proposed chronology of procedures for nominal time points when vital sign assessments coincide with other procedures.

Additional collection times, or changes to collection times of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.3. Electrocardiograms

Standard 12-Lead ECGs should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures pulse rate (PR), QT, and QTc intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. Triplicate ECGs will be collected at pre- and post-dose times at Visit 3, Visit 6, and Visit 9 as specified in the SoA.

If a postdose QTc interval remains ≥30 msec from the baseline **and** is >450 msec; or an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. Management of Glycemic Control

HAEs and fasting plasma glucose will be routinely monitored during participation in the study.

Based on this information, as well as review of the results reported by the central laboratory, an assessment of any symptomatic and asymptomatic occurrence of hypo- or hyper-glycemia must be undertaken.

8.2.4.1. Home Glucose Monitoring

- All participants will be provided home glucose monitoring supplies including a Sponsor-provided glucometer, instructions on the use of the glucometer and accompanying supplies.

- Home glucose monitoring logs will be provided to participants for completion at home and brought to each outpatient visit to the site along with the glucometers.

- For participants with T2DM, investigators must review the home glucose monitoring logs completed by the participants and the readings stored in the glucometer device at each visit to the site after the single-blind placebo run-in visit (Visit 2).

- For participants with obesity only, the review of the glucometer and glucose log should be completed if participants have signs or symptoms of hypoglycemia. Otherwise, regular glucometer monitoring at home is not required.

- Participants with T2DM must perform home glucose monitoring at least 3 times weekly following at least an 8- (preferably 10-) hour fast (except water). However, the investigator may recommend more frequent home glucose monitoring if needed.

- Less frequent glucose monitoring in participants with T2DM will NOT be considered a protocol deviation unless the participant fails to monitor his/her glucose for 3 or more days per week.

- If a participant experiences symptoms of hypoglycemia, home glucose monitoring should be performed, and these symptoms, along with the glucometer measurement, should be captured on the home glucose monitoring log.

- If a participant uses his/her own glucometer, and not one provided by the Sponsor, a protocol deviation will NOT be recorded provided the investigator is still able to monitor the participant's daily glucose values according to the criteria stated above.

8.2.4.2. Management of Hypoglycemia

Any episode of hypoglycemia must be captured on the Adverse Event CRF with specific details captured on the hypoglycemia Adverse Event (HAE) Form CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.2.4.2.1 below.

Participants noted to have a fasting glucose value (during home glucose monitoring) meeting the definition of hypoglycemia must be instructed to repeat the measurement the next day (following at least an 8- [preferably 10-] hour fast, except water). If the second measurement also meets the below definition, participants must be asked to return to the site within 1 to 3 days (following at least an 8- [preferably 10-] hour fast, except water) and have blood collected and sent to the central laboratory for analysis of fasting plasma glucose.

8.2.4.2.1. Definition and Severity of Categorization of Hypoglycemic Adverse Event (HAE)

Based on review of the participant completed home glucose monitoring log at each site visit, as well as results reported by the central laboratory, the investigator must assess the glucose values as well as any symptoms documented.

HAE is defined as **1** of the following:

1. **Asymptomatic hypoglycemia:** An event *not* accompanied by typical symptoms of HAE but a blood glucose value of <70 mg/dL (3.9 mmoL/L) using either glucometer (fingerstick blood glucose) or sponsor-identified central laboratory (plasma glucose).

2. **Documented symptomatic hypoglycemia:** An event during which typical symptoms of HAE are accompanied *with* a blood glucose value of <70 mg/dL (3.9 mmol/L) using glucometer (fingerstick blood glucose) or sponsor-identified central laboratory (plasma glucose) ***and*** the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or intravenous (IV) glucose.

3. **Probable symptomatic hypoglycemia:** An event during which symptoms of HAE are *not* accompanied by a glucose determination but was presumably caused by a blood glucose concentration of <70 mg/dL (3.9 mmol/L), ***and*** the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or IV glucose.

Each episode of HAE must be categorized with respect to severity. To characterize the event as severe, all **3** criteria below must be met:

1. The participant was unable to treat him/herself. Neurologic impairment, and not the age of the participant, is the explanation for why the participant could not treat him/herself and required the assistance of another person.

2. The participants exhibit at least one of the following neurological symptoms:

   - Memory loss;
   - Confusion;
   - Uncontrolled behavior;
   - Irrational behavior;
   - Unusual difficulty in awakening;
   - Suspected seizure;
   - Seizure;
   - Loss of consciousness.

3. Either:

   - If blood glucose was measured and was ≤54 mg/dL (2.7 mmol/L) using glucometer (or central laboratory); or
   - If blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

Events that do not meet all criteria above for severe HAE are characterized as mild or moderate in severity.

Any episode of HAE must be captured on the HAE CRF.

8.2.4.3. Management of Hyperglycemia

Hyperglycemia is defined as the following:

- Fasting blood glucose ≥270 mg/dL (15.0 mmol/L) using glucometer (or central laboratory).

After randomization, participants noted to have a fasting blood glucose value (during home glucose monitoring) meeting the above definition of hyperglycemia must be instructed to repeat the measurement the next day (following at least an 8- (preferably 10-) hour fast, except water). If the second measurement also meets the above definition, participants must be asked to return to the site a day later (following at least an 8- (preferably 10-) hour fast, except water) and have blood collected for fasting plasma glucose (and shipped to the central laboratory for analysis).

The investigator should determine if the participant collected the samples after an adequate fasting period; and if the participant is following recommended dietary guidelines. Proper dietary and collected procedures should be reinforced with the participant.

If the results from the central laboratory confirm the readings using glucometer, the participant should receive glycemic rescue medication at the discretion of the investigator (see Section 6.5.3).

8.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 to 35 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.6. Pregnancy Testing

Pregnancy tests will be both urine and serum tests, and must have a sensitivity of at least 25 mIU/mL. Serum pregnancy test will be required for eCRF collection. Urine pregnancy test will be used for site reference until serum pregnancy result becomes available. Pregnancy tests will be performed in all females at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the IP. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

8.2.7. Mental Health Questionnaires

8.2.7.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior.[19] The "baseline/screening" version of the C-SSRS will be administered at V1. The "since last visit" version of the C-SSRS will be administered at the other visits specified in the SoA. The C-SSRS will be administered by study site staff who have completed training in its administration. Participants who respond "yes" to questions 4 or 5 (indicating suicidal ideation), or to any suicidal behavioral question on the C-SSRS at V1, V2 or V3 will not be permitted in the study.

8.2.7.1.1. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet will be outlined in a guidance document provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.2.7.2. Patient Health Questionnaire-9 (PHQ-9)

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. A PHQ-9 score of ≥15 at V1, V2 or V3 indicates clinically significant depression and serves as an exclusion criterion for this study.

8.2.7.3. Referral to a Mental Health Professional

A participant should be referred to a MHP for the following reasons:

- Response of "yes" to question 4 or 5, or on any behavioral question on the C-SSRS;
- A score of ≥15 on the PHQ-9;
- In the investigator's judgment a risk assessment or exclusion is required.

A clinically-qualified MHP is a MHP with appropriate training in the assessment of suicide risk, according to local clinical practice standards and regulations, who would normally evaluate the risk for suicidal ideation and behavior in a patient.

Participants who have recurrent suicidal ideation or behavior during the study should be discontinued from the study and treated appropriately. If a study participant endorses a 4 or 5 on the ideation subscale or any behavioral item of the C-SSRS on 2 or more occasions and is confirmed to have active suicidal ideation or behavior on both occasions by a risk assessment conducted by a qualified MHP, then the participant should be discontinued from the study and treated appropriately.

Participants who meet criteria for referral to a MHP, but refuse evaluation and/or treatment by a MHP, must be assessed by the investigator to determine if the participant should be discontinued from dosing or from the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the study intervention (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving IP), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the IP.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to IP must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the IP under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 28 calendar days after the last administration of IP.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the IP by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the IP under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the IP;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of IP greater than 16 blinded tablets of PF-06882961 within a 24-hour time period ±2 hours will be considered an overdose.

There is no specific antidote for overdose with PF-06882961. Treatment of overdose should consist of general supportive measures.

In the event of an overdose, the PF-06882961 should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06882961 (whichever is longer).
3. Obtain a blood sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
5. Overdose is reportable to the Sponsor **only when associated with an SAE.** Refer to Section 8.3.4 for regulatory reporting requirements.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

In this study, blood samples (approximately 3 mL, each) to provide sufficient ***plasma*** for PK analysis will be collected into appropriately labeled tubes containing dipotassium edetic acid (ethylenediaminetetraacetic acid) - K_2 EDTA, at times defined in the SoA – with collections occurring ***prior to dosing with IP*** on the given scheduled visit and between 2 and 6 hours post dose on 3 different visits: Visit 3, Visit 6 and Visit 9. The date/time of the blood collection and the date/time of the previous ***2*** doses of blinded IP prior to **each** of the blood collections related to PK (both pre- *and* post- dose samples) should be noted in a dosing diary (or similar) by the participants and captured in the CRF.

- The PK samples must be processed and shipped as indicated in the study-specific laboratory manual provided to the investigator site, prior to initiation of study, to maintain sample integrity:
  - Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation;
  - Any *scheduled* pre-dose collection [ie, trough concentration (C_{trough})] obtained post dose **or** any post dose samples *not* collected within the 2-6 hours post dose interval, will be captured as a protocol deviation even if results are deemed evaluable.
- As part of understanding the PK of the IP, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data may not be included in the clinical report.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

8.6. Pharmacodynamics

PD parameters evaluated in this study include fasting plasma glucose, HbA1c and body weight and will be collected according to the SoA. The PD parameters of fasting plasma glucose and HbA1c will be assessed by the Central Laboratory as part of the clinical laboratory assessments (see Appendix 2), and body weight will be assessed as described in Section 8.6.1.

As part of understanding the PD of the IP, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical study report.

The PD samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.6.1. Body Weight

Body weight will be measured in duplicate as indicated in the SoA. The second weight measurement should be obtained at least 1-2 minutes apart from the first weight measurement.

Weight will be recorded using a calibrated scale (with the same scale used if possible for the duration of the study) reporting weight in either pounds (lb) or kilograms (kg), and accuracy to the nearest 0.2 lb (or 0.1 kg); ie, the device must be able to distinguish a difference between 150.4 lb (68.4 kg) versus 150.2 lb (68.3 kg). The scale must be placed on a stable, flat surface.

Weight measurement should be taken under the following conditions:

- Participant is in a fasted state (see Section 5.3.1);
- After void of urine;
- After removal of shoes, bulky layers of clothing and jackets so that only light clothing remains;
- While remaining still during the measurement.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

An approximately 4 mL blood sample optimized for DNA isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked biospecimens may be used for research related to drug response, T2DM and obesity. Genes and other analytes (eg, proteins, ribonucleic acid [RNA], nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked biospecimens to also be used to design and conduct research to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked biospecimens. The optional additional research does not require the collection of any further samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.8.1. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8.2. Banked Biospecimens for Biomarkers

Serum (Prep B2.5) and plasma (Prep B1.5) samples of approximately 6-mL each will be collected according to the SoA and as local regulations and IRB/ECs allow.

Banked biospecimens may be used for research related to drug response, T2DM, and obesity. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked samples to also be used to design and conduct research to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked samples. The optional additional research does not require the collection of any further samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

There are no estimands related to the primary objective and endpoint as outlined in Section 3.

A summary of estimands is provided in the table below and described in detail thereafter:

Variable	Estimand	Population	Intercurrent Event	Population-level Summary	International Council for Harmonisation (ICH)-E9(R1) Strategy(ies)
Fasting Plasma Glucose (continuous endpoint)	1A	T2DM on background of metformin	Absence of glycemic rescue medication and discontinuation of study IP	Mean difference (PF-06882961 versus Placebo)	Hypothetical While on treatment
	1B	Non-diabetic with obesity	Discontinuation of study IP	Mean difference (PF-06882961 versus Placebo)	Hypothetical While on treatment
HbA1c (continuous endpoint)	2A	T2DM on background of metformin	Absence of glycemic rescue medication and discontinuation of study IP	Mean difference (PF-06882961 versus Placebo)	Hypothetical While on treatment
	2B	Non-diabetic with obesity	Discontinuation of study IP	Mean difference (PF-06882961 versus Placebo)	Hypothetical While on treatment
Body Weight (continuous endpoint)	3A	T2DM on background of metformin	Absence of glycemic rescue medication and discontinuation of study IP	Mean difference (PF-06882961 versus Placebo)	Hypothetical While on treatment
	3B	Non-diabetic with obesity	Discontinuation of study IP	Mean difference (PF-06882961 versus Placebo)	Hypothetical While on treatment

Estimand 1A will be the population average treatment effect on the change from baseline in 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.[16]

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.

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.[16]

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:

Estimands 2A and 3A will utilize the same approach as Estimand 1A for the associated endpoints. Similarly, Estimands 2B and 3B will utilize the same approach as Estimand 1B for the associated endpoints.

Other exploratory/tertiary analyses may or may not be analyzed using these estimands and may be analyzed in a descriptive manner without reference to an estimand. Other estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of results, compare to available literature and/or be used for future study planning as needed. Details of these estimands and analyses will be presented in the SAP.

9.2. Sample Size Determination

A sufficient number of participants will be screened to achieve approximately 140 participants randomly assigned to IP (approximately 120 participants in a PF-06882961 arm and approximately 20 evaluable participants in the placebo arm). For participants with T2DM, approximately 20 participants will be allocated to each of the 5 PF-06882961 arms and approximately 15 participants will be allocated to the placebo arm. For non-diabetic participants with obesity, approximately 20 participants will be allocated to a PF-06882961 arm (Arm 7) and approximately 5 participants to the placebo arm. Assuming a 25% drop-out rate for the entire study population, approximately 140 participants will be randomly assigned to IP such that approximately 105 evaluable participants complete the study.

Once approximately 140 participants have been randomized into the study, enrollment will be halted and any participants who have signed the ICD and initiated screening procedures at this stage may be permitted to continue the study process to completion/withdrawal.

The number of participants was selected empirically to provide a sufficient number of participants to assess and characterize the safety and tolerability of various titration schemes and target doses of PF-06882961 across the 2 populations.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

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.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Pharmacodynamic Analyses

Endpoint	Statistical Analysis Methods
Secondary: Change from baseline in fasting plasma glucose at Weeks 2, 4, 6, 8, 10 and 12	A mixed model repeated measures (MMRM) analysis will be fitted to the change from baseline in fasting plasma glucose at Weeks 2, 4, 6, 8, 10 and 12 from the Estimand Set 1A to estimate the treatment effect related to the Estimand 1A. The MMRM 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. An unstructured correlation matrix will be used, and the Kenward-Roger approximation will be used for estimating degrees of freedom for the model parameters. Missing values will be imputed as part of the MMRM model assumptions. No adjustments will be made for multiplicity. The above analysis will also be applied separately to the Estimand Set 1B to estimate the treatment effect related to the Estimand 1B.

Secondary: Change from baseline in HbA1c at Weeks 2, 4, 6, 8, 10 and 12	Changes from baseline in HbA1c will be analyzed using a similar MMRM model to that used for fasting plasma glucose above. Baseline HbA1c will be included as a covariate in the model, rather than baseline fasting plasma glucose. No adjustments will be made for multiplicity. This analysis will be applied to the Estimand Set 1A to estimate the treatment effect related to Estimand 2A. It will also be applied separately to the Estimand Set 1B to estimate the treatment effect related to the Estimand 2B.
Secondary: Change from baseline in body weight at Weeks 2, 4, 6, 8, 10 and 12	Changes from baseline in body weight will be analyzed using a similar MMRM model to that used for fasting plasma glucose above. Baseline body weight will be included as a covariate in the model, rather than baseline fasting plasma glucose. No adjustments will be made for multiplicity. This analysis will be applied to the Estimand Set 1A to estimate the treatment effect related to Estimand 3A. It will also be applied separately to the Estimand Set 1B to estimate the treatment effect related to the Estimand 3B.
Tertiary/Exploratory	Will be described in the SAP finalized before database lock.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

All safety analyses will primarily report results by treatment arm, where Arms 6 and 7 will be reported as 2 separate groups (T2DM and non-diabetic participants with obesity) and Arm 5 will be reported as 2 separate groups (ie, Placebo will be reported separately across the 2 populations).

The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive IP (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations.

Endpoint	**Statistical Analysis Methods**
Primary	The primary endpoint will be analyzed in accordance with Pfizer Data Standards as above. The primary analyses will be on the incidence and severity of all treatment emergent adverse events (TEAE), that will be reported by treatment arm. The number of participants and percent will be presented.
Secondary	Secondary safety endpoints will also be analyzed in accordance with Pfizer Data Standards as above for the endpoints referenced in Section 3.

Additional exploratory safety analyses such as time to the first occurrence of AEs of interest (eg. diarrhea, nausea and vomiting, analyzed separately) and incidence of AEs of interest over time may also be performed (reported by treatment arm) where full details will be described in the SAP.

Results may also be reported by pooling the placebo groups or by strata (males vs. female), where details will be described in the SAP.

9.4.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized by treatment arm (as defined above in Section 9.4.2) and time.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTcF Assessment

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

9.4.3. Other Analyses

Tertiary/Exploratory analyses not included in the efficacy or safety analyses outlined above will be documented in the SAP and may not be reported in the CSR.

Pharmacogenomic or biomarker data from banked biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.5. Interim Analyses

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.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the IP, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative defined as legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICD.

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan (SMP).

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study team on demand (SToD) system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and IP identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 3. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine eGFR ***Plasma*** glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST ALT Total bilirubin GGT Alkaline phosphatase Uric acid Albumin Total protein	Urinalysis: • pH • Glucose (qual) • Protein (qual) • Blood (qual) • Ketones • Nitrites • Leukocyte esterase • Urobilinogen • Urine bilirubin • Microscopy[a] Urine pregnancy test	HbA1c Serum pregnancy test (β-hCG)[b] Lipid panel: • Total cholesterol • Direct LDL-C • HDL-C • Triglycerides TSH Free T4 Calcitonin Amylase Lipase ***Serum*** total bile acids PT/INR/aPTT <u>Screening only:</u> FSH[c] Urine drug screening C-peptide
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. For all female participants.
c. For all female participants to confirm post-menopausal status only.

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CO2 = carbon dioxide; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; GGT = gamma-glutamyl transferase; HbA1c = glycated hemoglobin; HDL-C = high density lipoprotein cholesterol; INR = international normalized ratio; LDL-C = low density lipoprotein cholesterol; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; qual = qualitative; RBC = red blood cell; TSH = thyroid stimulating hormone; WBC = white blood cell.

Investigators must document their review of each laboratory safety report.

Following screening, the sponsor study team and site will be blinded to HbA1c and fasting plasma glucose, measured by the central laboratory, unless the fasting plasma glucose meets the criteria for hypo-or hyper-glycemia as listed in Section 8.2.4.2 and Section 8.2.4.3.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from

baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the IP under

study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the IP under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and exposure during pregnancy [EDP] supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up

information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the IP caused the event, then the event will be handled as "related to IP" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will

be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below, during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s).

  The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

     - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - oral;
    - intravaginal;
    - transdermal;
    - injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - oral;
    - injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the IP; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the IP;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the IP prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the IP, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the IP.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- The samples may be analyzed as part of a multi study assessment of genetic factors involved in the response to PF-06882961 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for specified genetic analysis (see Section 8.6.1 and Section 8.8.2) will be stored indefinitely or other period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3× ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular contractions/complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40 bpm < x bpm <100 bpm), and

monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Prohibited Prior/Concomitant Medications

The following medications are prohibited until the first follow-up visit (ie, Visit 10, Week 13-14), unless stated otherwise. If a participant receives a prohibited medication, the investigator should contact the Sponsor Clinician or Sponsor Medical Monitor to determine if the participant may remain in the study.

Drug Classes and/or Drugs	**Timeframe of Restriction Prior to Screening Visit**
Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone.	90 days
Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, dulaglutide, semaglutide, pramlintide). ***Note***: Short-term (ie, ≤7 days) of insulin administration is permitted if participant is hospitalized.	90 days
Pharmacological agents with approved indication for weight loss such as liraglutide, orlistat and sibutramine.	90 days
Oral anti-diabetic medications, including: Sulfonylureas such as acetohexamide, chlorpropamide, tolazamide, tolbutamine, glimepiride, glipizide, glyburide. ***Note***: These may be used as glycemic rescue medications (See Section 6.5.3). Meglitinide analogues such as repaglinide, nateglinide. Dipeptidyl peptidase 4 inhibitors (DPP 4i) such as sitagliptin, saxagliptin, linagliptin, vildagliptin. α glucosidase inhibitors such as acarbose, miglitol. Sodium glucose cotransporter 2 (SGLT2) inhibitors such as canagliflozin, empagliflozin, dapagliflozin, ertugliflozin. ***Note***: These may be used as glycemic rescue medications (See Section 6.5.3). Anti-hyperglycemic medications, including bromocriptine and colesevelam.	60 days
Systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone. ***Note***: As an exception, steroid-containing inhalers, nasal sprays and topical formulations are permitted. ***Note***: Intercurrent treatment with systemic corticosteroids during participation in the study may be permitted if treatment does/will not exceed 7 days.	60 days
Immunosuppressants such as cyclosporine and tacrolimus.	60 days
Appetite or weight modifying medications, including nonprescription or herbals and medical grade marijuana.	60 days
Anti-psychotic medications such as olanzapine, risperidone.	60 days
Coumarin type anticoagulants or other anticoagulants (eg, dabigatran).	60 days
Anticonvulsants if prescribed for seizure disorder.	60 days

Drug Classes and/or Drugs	**Timeframe of Restriction Prior to Screening Visit**
Antiarrhythmic medications whose primary mechanism of action is sodium or potassium channel blockade (eg, procainamide, phenytoin, quinidine, proprafenone; as well as amiodarone, dofetilide, sotalol). ***Note***: β-adrenergic receptor blocking agents (eg, atenolol, metoprolol) and calcium channel blockers (eg, diltiazem, amlodipine, nifedipine) are permitted.	60 days
Sympathomimetic agents. ***Note***: Inhaled β-adrenergic receptor agonists (eg, albuterol) are permitted.	60 days
BCRP Substrates Rosuvastatin. ***Note***: Other statins are permitted. Sulfasalazine	Prohibited post randomization
Use of CYP3A4/5 substrates with narrow therapeutic index – eg, alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and terfenadine.	Prohibited post randomization
Use of chronic agents which are potent inducers of CYP3A (eg, rifampin, gemfibrozil, torsemide, amodiaquine).	Prohibited post randomization
Use of chronic agents which are clinically significant OATP inhibitors (eg, cyclosporine, gemfibrozil, rifampin).	Prohibited post randomization
Use of potent 3A4 inhibitors.	Prohibited post randomization
Paclitaxel.	Prohibited post randomization

10.9. Appendix 9: Proposed Chronology of Procedures

For the procedures described below, where multiple procedures are scheduled at the same timepoint(s) relative to dosing, the following chronology of events should be adhered to:

- 12-lead ECG: obtain prior to vital signs assessment, blood samples, and prior to dosing (except for post-dose collection) (see Section 8.2.3);
- Vital Signs (BP, Pulse Rate): obtain after 12-lead ECG collection but prior to obtaining blood samples and prior to dosing (except for post-dose collection) (see Section 8.2.2);
- Fasting blood samples [for safety (see Section 8.2.5, PK (see Section 8.5), exploratory biomarkers (see Section 8.8) and banked biospecimens (see Section 8.8.2)]: after assessment of 12-lead ECG and vital signs but prior to dosing;
- Body weight: obtain prior to dosing and food consumption (see Section 8.6.1);
- For the random, post dose PK blood collection to occur approximately 2 to 6 hours post dose (see Section 8.5): if collection time coincides with time of a meal/snack, these blood samples should be collected just prior to the meal/snack;
- Other pre-dose procedures: obtain sample/perform procedure as close as possible to the scheduled time, but may be obtained before or after blood sample collection(s);
- Dosing: must occur with food; and where applicable, after any pre-dose blood sample collection(s).

10.10. Appendix 10: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Abs	Absolute
AE	adverse event
ALT	alanine aminotransferase
AM	morning
aPTT	Activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{24}	area under the curve over 24 hours
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AV	Atrioventricular
BBS	Biospecimen Banking System
BCRP	Breast cancer resistance protein
β-hCG	beta-human chorionic gonadotropin
BID	Twice daily
BMI	Body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EC	Chronic Kidney Disease Epidemiology Collaboration
cm	Centimeter
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CR	Controlled release
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
C_{trough}	trough concentration
CV	Co-efficient of variance
%CV	percent Co-efficient of variance
CYP	Cytochrome P450
DDI	drug-drug interaction(s)
DILI	drug-induced liver injury
DMC	data monitoring committee

Abbreviation	Term
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase 4
DU	dispensable unit
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EFD	Embryo fetal development
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FPG	Fasting plasma glucose
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
HAE	Hypoglycemic AE
HbA1c	Glycolated hemoglobin A_{1c}
HDL-C	High density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	Identification
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IR	immediate release
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWR	interactive Web-based response
kg	kilogram

Abbreviation	Term
K_2 EDTA	ethylenediaminetetraacetic acid
lb	pound
LBBB	left bundle branch block
LDL-C	Low density lipoprotein cholesterol
LFT	liver function test
m^2	Meters squared
MAR	missing at random
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
msec	Millisecond
PM MDR1	multidrug resistance mutation
MEN2	multiple endocrine neoplasia syndrome type 2
MHP	mental health professional
mL	milliliter
MMRM	mixed model repeated measures
msec	millisecond
MTC	Medullary thyroid carcinoma
N/A	not applicable
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PACL	Protocol Administrative Letter
PCD	primary completion date
PD	pharmacodynamic(s)
PHQ-9	Patient Health Questionnaire-9
PI	principal investigator
PK	pharmacokinetic(s)
PM	afternoon
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	daily
QTc	corrected QT
QTcF	Baseline corrected QT interval (Fridericia method)
qual	Qualitative
Rac	accumulation ratio
RBC	red blood cell
SAE	serious adverse event
SGLT2	sodium glucose co-transporter 2
SoA	schedule of activities

Abbreviation	Term
SOP	standard operating procedure
SRSD	single reference safety document
SSID	Study specific identification
ST	slow titration
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
TBA	total bile acids
TBili	total bilirubin
TEAE	Treatment emergent adverse event
TI	therapeutic index
T_{max}	Time to maximum concentration
TSH	Thyroid stimulating hormone
TZDs	thiazolediediones
$T_{1/2}$	Half-life
T2DM	type 2 diabetes mellitus
UGT	uridine 5'-diphospho-glucuronosyltransferase glucuronosyltransferase
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	woman of childbearing potential

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