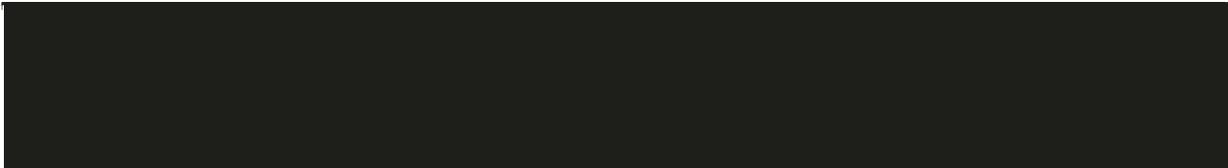




**A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN,
PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY, TOLERABILITY,
PHARMACOKINETICS, AND PHARMACODYNAMICS OF MULTIPLE
ESCALATING ORAL DOSES OF PF-06882961 IN ADULT SUBJECTS WITH
TYPE 2 DIABETES MELLITUS**

Investigational Product Number:	PF-06882961
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [REDACTED]
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SCHEDULE OF ACTIVITIES

The schedule of activities tables (both [Table 1](#) and [Table 2](#)) provide an overview of the protocol visits and procedures. Refer to [Section 6](#) and [Section 7](#) 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 schedule of activities tables, in order to conduct evaluations or assessments required to protect the well-being of the subject. Abbreviations found in [Appendix 1](#).

- a. Day relative to first dose of investigational product (Day 1).
- b. Discharge from CRU.
- c. Full physical exam at Screening, Day 15, Day 29, and early termination visit (if appropriate); otherwise, limited exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.
- d. 12-lead ECG at Screening, Day 30, Follow-up, and early termination visit (if appropriate) are single; all other study days, collect triplicate ECGs. Triplicate ECGs should be conducted prior to AM dose at 0H and at approximately 4H (estimated T_{max}) after AM dose on Days 2, 4, 8, 11, 15, 18, 22, and 25. On Day 29, triplicate ECG collected at 0H only. When a meal or snack is scheduled at the same time as an ECG, the ECG must be performed prior to the meal/snack.
- e. Includes blood pressure and pulse rate; vital signs at Screening, Day 30, Follow-up, and early termination visit (if appropriate) are single; all other times, collect triplicates prior to AM dose at 0H and additional triplicates at approximately 4H (estimated T_{max}) after AM dose on Days 2, 4, 8, 11, 15, 18, 22, and 25. On Day 29, triplicate vital signs collected at 0H only.
- f. On Day -2, glucometer measure should be obtained on admission to CRU. Glucometer measures on Days -1 through 30 should be obtained prior to breakfast. Measurements may be taken more frequently at the discretion of the investigator.
- g. Meals to be provided at approximately 0H, 4H, and 10H after AM dose; snacks may be provided, at time specified in [Table 2](#).
- h. Dosing to occur BID with breakfast and dinner. For QD regimen, if administered, dosing to occur with breakfast only, at time specified in [Table 2](#).
- i. Collection following fasting duration as specified in [Section 4.4.1](#).
- j. **CCI** [REDACTED]
- k. In females to confirm postmenopausal status only.
- l. PK samples to be collected prior to AM dose and at 4H after AM dose on Days 8 and 18. Day 29 samples to be collected at 36H after AM dose on Day 28. Day 30 sample to be collected 48H after AM dose on Day 28.

Table 2. Schedule of Activities – Study Days -1, 1, 14, 21 & 28

[Procedures at 0H to be completed prior to dosing or similar clock time, in the case of Day-1]

Hours Relative to Dosing at 0H^a	0	0.25	0.5	1	1.5	2	3	4	6	8	10	12	14	24
Continued inpatient stay at CRU	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse event monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Body weight (Days -1, 14, and 28 only)	x													
Triplicate, supine 12-lead ECG	x			x		x		x		x		x		
Triplicate, supine vital sign assessment ^b	x			x		x		x		x		x		
Glucometer measurement ^c	x													
Mixed meal tolerance test (Days -1, 14, and 28, only)	x													
Standardized meal/snack ^d	x ^e							x			x		x	
Blinded investigational product administration QD or BID (Days 1, 14, 21, and 28 only)	x ^f										x ^g			
Blood sampling for:														
- Safety laboratory tests (Days -1, 14, 21, and 28 only) ^h	x													
- Banked biospecimen Prep D1.5 (Day 1 only) ⁱ	x													
CCI														
- HbA1c, TSH (Day -1 and 28 only)	x													
CCI														
- Free T4, calcitonin, amylase, lipase, total bile acids, lipids (Days -1, 14, and 28 only)	x													
- PF-06882961 PK (Days 1, 14 or 21[depending on Cohort] ^k , and 28 only)	x ^{h,i}			x		x		x ^l	x	x	x	x	x	x
- Metabolite scouting (0H on Day 1 and all time points on Day 28)	x					x		x		x		x ^m		x ^m
Urine sampling for:														
- Urinalysis and microscopy, as appropriate (Days 1, 14, 21, and 28 only)	x													
- PK predose spot urine (urine blank) (Day 1 only)	x													
- PF-06882961 PK (Day 28 only)	x	→	→	→	→	→	→	→	→	→	→	→	→	x ⁿ

- a. On Day -1, nominal time to match approximate clock time of collection planned on Day 1 to permit time-matched comparison.
- b. Includes blood pressure and pulse rate at all time points.
- c. Glucometer measures taken before breakfast on all days while inpatient.
- d. Meals/snacks to occur on all days while inpatient; identical meals/snacks on Days -1, 14, and 28.
- e. Standard breakfast on Day 1 and 21 only.
- f. Dosing expected to occur with breakfast or mixed meal.
- g. Dosing expected to occur with dinner (BID regimen only).
- h. [REDACTED]
- i. [REDACTED]
- j. [REDACTED]
- k. PK samples obtained at all listed timepoints on Day 1 and Day 28 for all cohorts. For Cohorts 1 & 2, PK samples obtained at all listed timepoints on Day 14 (*not* Day 21). For Cohorts 3 & 4, PK samples obtained at all listed timepoints on Day 21 (*not* Day 14). For Cohort 5 and optional Cohorts (if used), decision to obtain PK samples on Day 14 or Day 21 will be provided in writing prior to initiation of dosing for those cohorts.
- l. For Cohorts 1 & 2, on Day 21 *only*, PK samples will be obtained at 0H and 4H. For Cohorts 3 & 4, on Day 14 *only*, PK samples will be obtained at 0H and 4H. For Cohort 5 and optional Cohorts (if used), decision to obtain PK samples at only 0H and 4H on Day 14 or Day 21 will be provided in writing prior to initiation of dosing for those cohorts.
- m. For optional QD regimen *only* (if utilized), metabolic scouting samples to be collected at 12H and 24 H post-dose on Day 28.
- n. Urine collection for PK to occur over 0-24H.

1. 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 the injectable peptidic GLP-1R agonists that are approved for the treatment of type 2 diabetes mellitus (T2DM).

The purpose of this study is to characterize the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of multiple oral doses of PF-06882961 in adult subjects with T2DM.

1.1. Mechanism of Action/Indication

PF-06882961 is an oral GLP-1R agonist that is currently being developed as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

1.2. 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 380 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.

Based on the successful 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.

1.2.1. Nonclinical Pharmacology

In vitro primary PD studies demonstrated that, in cells expressing recombinant human and cynomolgus monkey GLP-1R, PF-06882961 dose-dependently promotes 3'-5'-cyclic adenosine monophosphate (cAMP) production with concentrations corresponding to 50% of the maximum effect (EC₅₀) of 11.7 and 12.3 nM, respectively. In contrast, no cAMP production was observed in cells expressing recombinant rat, mouse, and rabbit GLP-1R at tested concentrations (EC₅₀ >10-20 μM). PF-06882961 was shown to bind to the human GLP-1R with a mean binding inhibition constant (K_i) of 80.1 nM using a competition binding assay. In vivo, PF-06882961 potentiated glucose-stimulated insulin secretion during an intravenous glucose tolerance test (IVGTT) in cynomolgus monkeys in a dose- and concentration-dependent manner. Finally, PF-06882961 was also shown to reduce food intake in cynomolgus monkeys. In all in vivo studies, efficacious plasma levels were consistent with the in vitro potency.

1.2.2. Nonclinical Pharmacokinetics and Metabolism

Single-dose PK studies with PF-06882961 were conducted after intravenous (IV) and oral administration to rats and nonhuman primates. The toxicokinetics (TK) of PF-06882961 were determined in 1-month repeated oral dose toxicity studies in male and female rats, and in a 6-week toxicity study in male and female nonhuman primates. The fraction unbound (f_u) of PF-06882961 in rat, nonhuman primates, and human plasma was 0.0178, 0.0182, and 0.0293, respectively. PF-06882961 is a substrate for organic anion transporting polypeptides (OATP)1B1, OATP1B3, and OATP2B1, multi-drug resistance protein (MDR)1 (also known as P-glycoprotein; P-gp), and breast cancer resistant protein (BCRP) in vitro. PF-06882961 is expected to be cleared via hepatic uptake by OATP, followed by metabolic elimination by cytochrome P450 (CYP) enzymes. The metabolic clearance pathway for PF-06882961 in humans is principally mediated by cytochrome P450 (CYP) (72%), with a major contribution from CYP3A4/5 (50%) and minor contributions from CYP2C8 (13%) and CYP2C19 (9%) as determined in cryopreserved human hepatocytes. The in vitro and in vivo metabolic profile of PF-06882961 in the preclinical toxicity species (rat and nonhuman primates) and human hepatocytes was similar across species, with no evidence of human specific metabolites.

The in vitro inhibitory potential of PF-06882961 against major human CYP and uridine glucuronosyl transferase (UGT) enzymes has been characterized in human liver microsomes (HLM). Potential for drug-drug interaction (DDI) was evaluated using the projected unbound intestinal lumen or liver concentrations at the anticipated range of doses to be examined in this study. PF-06882961 is a weak time- and nicotinamide adenine dinucleotide phosphate-oxidase (NADPH)-dependent inhibitor of CYP 3A4/5 activity, and there is a potential for interaction with relevant sensitive substrates at PF-06882961 doses where projected area under the curve from time 0 to 24 hours (AUC₂₄) exposure is expected to exceed approximately 7392 ng·h/mL. Based on preliminary modeling of PK data emerging from the ongoing first-in-human (FIH) study, this AUC₂₄ is currently predicted to be achieved at doses exceeding 300 mg twice daily (BID, [Table 5](#)), although this dose level may be refined based on emerging data from this study. In addition, PF-06882961 is a reversible inhibitor of CYP2C8 and UGT1A1, suggesting that there may be a potential for interaction

over the anticipated range of doses to be examined in this study with drugs that are primarily metabolized by these enzymes.

The potential for PF-06882961 to inhibit various uptake and efflux drug transporters was evaluated in stably expressed mammalian cellular systems or vesicle-based transporter systems. Evaluation of the DDI potential, using the projected unbound intestinal lumen or portal inlet concentrations at the anticipated range of doses to be examined in this study, suggests that there may be a potential for interaction with drugs (eg, rosuvastatin) that are subject to active intestinal/hepatic uptake by OATP2B1/1B1 and/or intestinal efflux mediated by BCRP.

1.2.3. Nonclinical Safety

In the 6-week general toxicology study in nonhuman primates at doses of 50, 75, and 100 mg/kg/day, no adverse findings were observed at any of the administered dose levels. Test article-related, but nonadverse findings were observed at all doses including slightly decreased food consumption, transiently decreased body weight in females, sporadic emesis, decreased systolic, diastolic and/or mean blood pressure (BP), and alterations in select hematology and clinical chemistry parameters. In a single-dose cross-over safety pharmacology cardiovascular study in nonhuman primates, nonadverse increases in BP, heart rate, and left ventricular contractility were noted at ≥ 75 mg/kg (unbound maximum observed concentration [C_{max}] 23.0 ng/mL and area under the curve from time zero to 24 hours [AUC_{24}] 206 ng•h/mL) and increased corrected QT interval (QTc) was noted at 250 mg/kg.

The only nonclinical species for which PF-06882961 activates the GLP-1 receptor is the nonhuman primate; therefore, toxicology studies in rats were used to evaluate off-target pharmacology. In oral toxicity studies in rats up to 1-month in duration, adverse findings were observed only at the highest dose of 1000 mg/kg/day, which was not tolerated due to mortality and unscheduled euthanasia secondary to decreased food consumption, decreased body weight, and moribund condition. Adverse microscopic findings in this study at 1000 mg/kg/day were noted in the heart (mild to moderate degeneration/necrosis of cardiomyocytes), thymus (decreased lymphocyte cellularity, secondary to stress), stomach (erosion or ulcer), and Harderian gland (acinar necrosis and neutrophilic inflammation).

At 1000 mg/kg/day, test article-related, but nonadverse findings included heart (vacuolation of cardiomyocytes), cecum (single cell necrosis of epithelial cells), Harderian gland (degeneration/regeneration), kidney (vacuolation of tubular epithelium associated with higher creatinine and blood urea nitrogen), liver (hepatocellular hypertrophy), salivary gland (atrophy or single cell necrosis of acinar cells), and adipose tissue (decreased lipid content).

There were no adverse test article-related findings at doses up to 500 mg/kg/day for 1 month. Minimal cardiomyocyte degeneration/necrosis noted in 2/20 animals at 250 mg/kg/day and 1/6 males surviving to scheduled necropsy at 1000 mg/kg/day was not considered adverse due to the minimal severity and limited distribution. However, this finding was not observed in a subsequent 1-month study in rats up to 500 mg/kg/day. Other nonadverse findings were noted at ≥ 150 mg/kg/day in the cecum and at ≥ 250 mg/kg/day in the liver (hepatocellular vacuolation associated with higher total bilirubin [Tbili] and hepatobiliary enzymes), thyroid

(alterations in thyroid hormones and hypertrophy of follicular cells), and pancreas (decreased zymogen content). Alterations in clinical laboratory parameters, including increased total plasma bile acids, were also observed.

PF-06882961 did not induce micronuclei in the reticulocytes from peripheral blood of male and female rats at doses of 50, 250, or 1000 mg/kg/day. PF-06882961 was negative for the potential of phototoxicity in the neutral red uptake phototoxicity study in BALB/c 3T3 fibroblasts. PF-06882961 was negative in all genetic toxicity assays and was monitored in the pivotal in vivo toxicity and safety pharmacology studies.

The no observed adverse effect level (NOAEL) in the pivotal 6-week toxicity study in nonhuman primates was 100 mg/kg/day (mean combined-sex unbound C_{max} 24.2 ng/mL and AUC_{24} 175 ng•h/mL), and the NOAEL in a pivotal 1-month toxicity study in rats was 500 mg/kg/day (mean combined-sex unbound C_{max} 767 ng/mL and AUC_{24} 5856 ng•h/mL).

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB).

1.2.4. Preliminary Summary of Clinical Experience with PF-06882961

As of the issuance of this protocol, there is 1 ongoing clinical study, C3421001, which is the first to administer PF-06882961 to humans. C3421001 is an investigator- and subject-blinded (sponsor-open), randomized, placebo-controlled, single ascending oral dose, study conducted at 1 clinical research unit (CRU). To date, 25 healthy adult subjects (men and women of non-childbearing potential) have been randomized to receive PF-06882961 or placebo in 3 cohorts, and each subject has participated in up to 4 crossover periods.

Cohorts 1 (n=8) and 2 (n=9) were conducted with an interleaving, dose-escalation design. Subjects were administered single doses of PF-06882961 or placebo in the fasted state, except 1 period administered in the fed state with a high fat breakfast. Cohort 3 (n=8) was administered split doses of PF-06882961 or placebo, administered 8 hours apart, in the fed state with standard breakfast and snack. PF-06882961 or placebo was administered as an immediate release (IR) tablet for all periods except 1 period for Cohort 1, which was administered as an IR oral solution. Draft preliminary safety and PK data from the 4 periods of Cohorts 1, 2 and 3 are currently available.

As this study is ongoing, all data presented here are preliminary and subject to change. To date, PF-06882961 has demonstrated an acceptable safety profile, and there have been neither serious adverse events (SAEs) nor adverse events (AEs) of severe intensity reported. Overall, no adverse, clinically significant changes in safety laboratory parameters, electrocardiograms (ECGs), and vital signs have been observed. Over the dose range of 3 mg to 300 mg administered in Periods 1-4 for Cohorts 1-3, a total of 100 AEs were reported. The majority (95) was mild in severity and 5 were moderate in severity. The most frequently encountered AEs were related to the gastrointestinal (GI) system and included nausea, anorexia, and vomiting.

An overview of PF-06882961 plasma PK parameters based on preliminary data observed following single-dose, oral administration of IR tablets and an IR oral solution is given in [Table 3](#) and [Table 4](#).

Table 3. C3421001: Observed Preliminary PK Parameters, PF 06882961 Cohorts 1 and 2

Dose/Cohort/ Conditions	Cmax Geometric Mean ng/mL (%CV)	Tmax Median hr (range)	AUClast Geometric Mean ng.h/mL (%CV)	t1/2 Arithmetic Mean hr (%CV)
3 mg/ Cohort 1/ IR tablet fasted	6.4 (59.1)	2 (1.25-4)	39.2 (53.5)	3.17 (34.9)
10 mg/ Cohort 2/ IR tablet fasted	13.2 (53.6)	6 (3-6)	86.4 (53.8)	4.01 (20.4)
25 mg/ Cohort 1/ IR solution fasted	52.3 (50.2)	2 (1.25-2)	271 (28.5)	4.64 (26.9)
30 mg/ Cohort 1/ IR tablet fasted	41.2 (62.4)	4 (1.25-6)	297 (44.8)	4.52 (36.4)
100 mg/ Cohort 2/ IR tablet fasted	176 (91.4)	6 (0.75-6)	1120 (46.9)	5.78 (35.2)
100 mg/ Cohort 2/ IR tablet high-fat meal	76.8 (23.3)	6 (6-12)	918 (52.2)	4.86 (17.9)
300 mg/ Cohorts 1+2/ IR tablet fasted	732 (91.2)	4 (0.3-12)	4810 (44.5)	5.55 (27.6)

NOTE that these parameters have been calculated based on preliminary data from the ongoing C3421001 study using planned sample collection times and are subject to update on final reporting. %CV = percent coefficient of variance

Table 4. C3421001: Observed Preliminary PK Parameters, PF 06882961 Cohort 3

Dose	Cmax _{0-8H} Geometric Mean ng/mL (%CV)	Tmax _{0-8H} Median hours (range)	Cmax Geometric Mean ng/mL (%CV)	Tmax Median hours (range)	AUClast Geometric Mean ng.h/mL (%CV)	t1/2 Arithmetic Mean hours (%CV)
20+20 mg (40 mg split)	29.4 (26)	6 (4-6)	35.8 (34.7)	12 (6-12)	491 (26.7)	5.33 (23.6)
50+50 mg (100 mg split)	62.4 (44.5)	6 (2-8)	84.9 (33.9)	12 (6-14)	1260 (42)	5.12 (15.6)
150+150 mg (300 mg split)	126 (33.8)	6 (6-6)	199 (36.3)	12 (6-24)	3810 (28.7)	5.62 (28.8)
200+100 mg (300 mg split)	144 (46.8)	6 (6-8)	268 (86.7)	10 (6-24)	3900 (39.5)	5.22 (17.8)

NOTE that these parameters have been calculated based on preliminary data from the ongoing C3421001 study using planned sample collection times and are subject to update on final reporting.

Cohort 3 conditions: IR tablet administered at 0H with standard breakfast and at 8H with snack.

%CV = percent coefficient of variance

1.3. Rationale

1.3.1. Study Rationale

The purpose of this study is to evaluate the safety, tolerability, and PK of multiple oral doses of PF-06882961 in adult subjects with T2DM. The study will also assess the effect of repeated, oral doses of PF-06882961 on PD biomarkers, CCI [REDACTED]

The study includes 5 planned cohorts, with 3 optional cohorts to permit thorough exploration of the dose range along with potential assessment of dosing (including once daily [QD] and/or BID administration) and/or titration regimens, as informed by emerging safety, tolerability, PK, or PD data from this study. PF-06882961 will be administered via the IR tablet formulation for a majority of the cohorts. CCI [REDACTED]

Given that the current study is the first to administer repeated doses of PF-06882961 to humans, an escalating design with careful on-going review of safety and PK of PF-06882961 is proposed. A baseline day (Day -1) with time-matched procedures will permit an improved assessment of safety, tolerability, as well as PD effects, ie, change from baseline (CFB, within subject) and placebo-adjusted comparison of dose-response (between subject), as appropriate. The subjects and site staff (except those involved in the preparation of doses) will be blinded to administration of active versus placebo in each cohort to permit an unbiased assessment of safety. However, a limited number of members of the Sponsor team will be unblinded to permit a real-time review of safety and tolerability in order to assess potential for drug-induced changes.

Total duration of dosing PF-06882961/placebo in this study is proposed for up to 4 weeks, as supported by completed nonclinical toxicity studies in rats and nonhuman primates. Dose titration is anticipated to be included in most cohorts to enhance tolerability to higher doses of PF-06882961. In the 5 planned cohorts, at least 2 weeks of dosing at each target dose level is anticipated. This duration is expected to permit sufficient assessment of safety, tolerability, PK and PD of PF-06882961.

Clinical safety laboratory tests, thorough assessments of vital signs and 12-lead ECGs, physical examinations, and AE monitoring will provide essential data to evaluate the safety and tolerability of PF-06882961. CCI [REDACTED]

In an effort to reduce variability and better quantify potential changes in heart rate and BP during the study, all measurements of ECG, heart rate and BP will be collected in triplicate (except as noted in the [Schedule of Activities](#)) and the mean heart rate and mean systolic and diastolic BP will be used for analysis at each time point. In addition to triplicate BP

measurements taken prior to dosing of investigational product (IP), metformin, and any morning dose of permitted concomitant medications, triplicate BP measurements will also be collected at approximate time for C_{max} (T_{max}) on PK sampling days as specified in the [Schedule of Activities](#) to further enhance quantification of any possible drug effect.

As part of the clinical safety laboratory tests, calcitonin, amylase, and lipase will be assessed, as these laboratory parameters have been shown to increase in patients treated with marketed GLP-1R agonists.¹⁰ In addition, thyroid stimulating hormone (TSH), free thyroxine (FT4), lipids, coagulation profile, and total bile acids will be assessed, based on non-adverse findings in the nonclinical studies with PF-06882961 (see [Section 1.2.4](#)). CCI [REDACTED]

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 at least once daily (pre-breakfast), and careful monitoring of symptomatic hypoglycemic AEs will be performed.

Dosing of PF-06882961 is planned to occur in the fed state, ie, with breakfast in all dosing regimens and with dinner for BID dosing regimens. If thought necessary to achieve study objectives (eg, to assess tolerability or exposure), the timing of meals or snacks relative to study treatment administration may be altered during any of the study cohorts; should this be necessary, details will be provided to investigators in writing.

1.3.1.1. Study Population

The population for this study will be male and female adult subjects with T2DM. Female subjects will be confirmed as women of non-childbearing potential since, at the present time, embryo-fetal developmental toxicology studies with PF-06882961 have not been conducted. In male subjects, appropriate measures to minimize potential transfer of PF-06882961 via semen to a partner are required (refer to [Section 4.4](#)).

Subjects enrolled in this study will have inadequately controlled T2DM (as indicated by HbA1c at screening) on metformin monotherapy, which is considered first-line therapy for glycemic control according to current treatment guidelines.¹² At screening, this study requires that subjects have been taking a minimum stable metformin dose of ≥ 500 mg/day for at least 2 months prior to the screening visit. The dose of metformin, where possible, is expected to remain the same until completion of study participation (ie, Follow-up visit). A clinical drug-drug interaction (DDI) study with metformin has not been conducted at this time, as in vitro data suggest that PF-06882961 is not expected to impact the PK of metformin via inhibition of organic cation transporter (OCT)2, and the risk of a clinical interaction is deemed negligible.

In addition, subjects will be allowed to take certain concomitant medications as outlined in [Section 5.8](#).

1.3.1.2. Pharmacokinetic Parameters

As is typical for multiple ascending dose (MAD) studies with investigational agents, this study will include plasma sampling to examine the Day 1 and steady-state PK of PF-06882961. Urine samples will also be collected to evaluate the proportion of drug excreted via renal elimination. Plasma PK and urine samples will be collected for exploratory metabolite identification.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

1.3.2. Dose Rationale

1.3.2.1. Prediction of Efficacious Dose/Concentration

A clinically efficacious dose of PF-06882961 should provide HbA1c lowering over 12 weeks of at least 1% from a baseline of 8.0%, assuming a background of anti-hyperglycemic medications. Using preliminary modeling of PK data emerging from the ongoing FIH study, this dose is predicted to be approximately 131 mg BID, which is projected to yield an average unbound efficacious concentration (C_{eff}) of approximately 6.9 nM (130 ng/mL total), at steady state.

1.3.2.2. Selection of Dose Levels

The nonclinical safety profile of PF-06882961 was adequately characterized to support progression into human clinical studies encompassing dosing periods up to 4 weeks in duration (see [Section 1.2.3](#)).

The doses proposed for this study were determined considering all relevant information obtained from nonclinical safety studies along with preliminary safety, tolerability, and PK data observed in the ongoing study C3421001.

A starting dose of 15 mg PF-06882961 BID is planned. At this dose, the projected average concentration of PF-06882961 at steady-state is approximately 9-fold below the projected C_{eff} (see [Section 1.3.2.1](#)). Based on preliminary data from study C3421001 ([Section 1.2.4](#)), this dose is expected to have an acceptable safety and tolerability profile.

The dose range for this study was chosen in order to appropriately bracket the projected efficacious dose to cover the potential impact of uncertainty in projection of efficacious concentration or of unanticipated factors on drug exposure, while accommodating feasibility considerations including tablet burden. The highest planned dose will be identified as the dose deemed to be the maximum tolerated dose (MTD) upon repeated administration or a total daily dose of 1600 mg (800 mg BID), whichever is the most conservative. At steady state, a dose of 800 mg BID is projected to yield an average concentration approximately 6-fold above the projected C_{eff} (see [Section 1.3.2.2](#)) and is projected to yield C_{max} and AUC_{24} exposures approximately 16- and 11-fold below the defined human exposure limits ie, the NOAEL in a 4-week toxicology study in rats (see [Section 1.2.3](#) and [Section 3.2](#)).

Dose escalation to the NOAEL in the 4-week toxicology study in rats is proposed due to the fact that no adverse findings were noted at the highest dose administered in nonhuman primates and that nonadverse findings such as decreased food intake were reversible in the nonhuman primates and are monitorable in a clinical setting ([Section 1.2.3](#)). Predicted exposure levels and safety margins for a range of anticipated doses for this study are provided in [Table 5](#) below. All exposure-based safety margins were calculated using unbound concentrations. This table gives an overview of the potential dose levels however the increment of C_{max} and AUC_{24} between dose levels will be targeted to be approximately semi-logarithmic.

Table 5. A Selection of Potential Doses, Predicted Human Exposure at Steady State, and Safety Margins with Administration of Multiple, Oral Doses of PF-06882961

Proposed Dose (mg)	Total C _{max} (ng/mL) ^a	Total AUC ₂₄ (ng/h/mL) ^a	Predicted C _{max} Safety Margin ^b	Predicted AUC ₂₄ Safety Margin ^b
15 mg BID	32.2	360	813	555
50 mg BID	109	1202	240	166
150 mg BID	321	3600	81.5	55.5
300 mg BID	650	7392	40.3	27.0

- Predicted steady state exposure following 14 days of dosing at target daily dose.
- Relative to free (human $f_u = 0.0293$) PF-06882961, C_{max} of 767 ng/mL and AUC₂₄ of 5856 ng·h/mL at the NOAEL dose in a 1-month toxicity study in rats.
- Predicted exposures presented for doses proposed for Cohorts 1-4. Doses for Cohort 5 and optional cohorts (if studied) are to be determined (TBD).
- While a selection of potential doses is presented in this table, the increment of C_{max} and AUC₂₄ in dose escalation will be targeted to be no more than approximately semi-logarithmic. Dose escalation rules are summarized in [Section 3.2](#).

See [Section 1.2.2](#), [Section 1.2.3](#), and [Section 1.3.2.1](#).

1.3.2.3. Dose Titration

All cohorts in this study will complete a total of 28 days of dosing. Cohort 1 will be dosed with 15 mg BID or placebo BID for all 28 days with no titration. For the planned Cohorts 2-5, it is expected that these cohorts will require up to approximately 2 weeks of titration, in addition to at least 14 days of dosing at the target dose level, and a sample dosing titration scheme is shown in [Table 6](#). This sample titration scheme is provided for illustrative purposes only, and dose titration paradigms specified in [Table 6](#) may be modified based on the emerging safety, tolerability, or PK data. For optional cohorts, additional titration schemes, including up to 4 weeks of dose titration without a dosing period at a target dose level, may be explored. The total duration of dose administration in any given subject will not exceed 28 days. The dose titration schedule will be provided in writing prior to the start of each cohort, whether planned or optional.

During the titration period, if a subject does not tolerate titration to the next dose level, as determined by the principal investigator (PI) and with notification to the Sponsor, the subject may be reverted to the previously tolerated dose level, and dose titration to the next higher dose may be delayed by 1 to 2 days or longer, as needed.

Following down-titration, 2 separate attempts at up-titration to the next dose level are permitted, per investigator discretion. If, per investigator assessment, unacceptable intolerance (eg, severe vomiting) occurs shortly following dose administration, the dose will not be readministered and the subject will resume dosing at the next scheduled dosing time. Subjects whose dose level is tolerability-limited may continue in the study for the intended duration of their assigned cohort (with 28 days dosing in total) at their own individual MTD, as judged to be appropriate by the PI and Sponsor. For Cohorts 2-5, titration will ***not*** be permitted after Day 14 and subjects should remain on the same dose (even if lower than the target dose) from Days 15-28.

Actual doses, titration dosing schedules and target exposures may be adjusted during the study based on emerging human safety and PK data but will not be predicted to exceed the PK stopping limits of a total C_{max} of 26177 ng/mL and a total AUC_{24} of 199860 ng·h/mL, as listed in [Section 3.2](#).

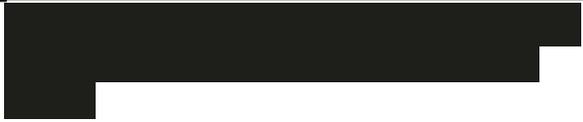
Table 6. Sample Titration Scheme and Dosing Paradigm

Cohort ^a	Study Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 through 28 ^b
1	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID	15 mg BID
2	15 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID	50 mg BID
3	15 mg BID	50 mg BID	100 mg BID	150 mg BID or MTD ^c											
4	15 mg BID	50 mg BID	100 mg BID	150 mg BID	200 mg BID	250 mg BID	300 mg BID or MTD								
<p>a. Doses and dose titration approaches for Cohort 5 and optional cohorts (if studied) are to be determined (TBD).</p> <p>b. Dosing administered from Days 15 through 28.</p> <p>c. For subjects not able to reach to target dose of that cohort, the individual MTD for that subject may be permitted.</p> <p>For all dosing and titration regimens, matching placebo will also be administered.</p>															

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	Primary Endpoints:
<ul style="list-style-type: none"> To evaluate the safety and tolerability of ascending, multiple, oral doses of PF-06882961, administered to adult subjects with T2DM. 	<ul style="list-style-type: none"> Assessment of AEs, safety laboratory tests, vital signs and 12-lead ECGs.
Secondary Objectives:	Secondary Endpoints:
<ul style="list-style-type: none"> To characterize plasma pharmacokinetics of PF-06882961 following Day 1 and following multiple, oral doses administered to adult subjects with T2DM. 	<ul style="list-style-type: none"> PF-06882961 plasma pharmacokinetic parameters AUC_{24}, C_{max}, T_{max}, $t_{1/2}$ (as defined in Section 9.3.1, as appropriate for the dosing paradigm) following Day 1, and multiple dose administration, as data permit.
<ul style="list-style-type: none"> To characterize the PK of PF-06882961 in urine following multiple, oral doses administered to adult subjects with T2DM. 	<ul style="list-style-type: none"> Urine PK parameters for PF-06882961, as data permit: Ae_{24}, $Ae_{24}\%$, and CLr.

<p>CCI [REDACTED]</p>	<p>[REDACTED]</p> <ul style="list-style-type: none">[REDACTED][REDACTED]
<p>[REDACTED]</p>	<p>[REDACTED]</p> <ul style="list-style-type: none">[REDACTED][REDACTED][REDACTED]
<p>[REDACTED]</p>	<p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p>

3. STUDY DESIGN

3.1. Study Overview

This is a randomized, double-blind (sponsor-open), parallel, placebo-controlled, multiple oral dose-escalating study of PF-06882961 in subjects with T2DM on a background of metformin monotherapy.

Subjects will receive oral doses of PF-06882961 or placebo in this study. A total of approximately 12 subjects (9 active and 3 placebo) will be enrolled in each cohort, for a total of approximately 60 (Cohorts 1-5) or up to approximately 96 (if including optional Cohorts 6-8) subjects randomized. As a result, the maximum number of cohorts in the study will not exceed 8, corresponding to a maximum of 96 completed subjects. The randomization ratio within a cohort will be 3:1 between PF-06882961 and placebo. The study will be conducted at approximately 2-5 clinical sites in the US. Attempts will be made to equally balance the enrollment of subjects to active and placebo across sites within each cohort. It is not necessary for every site to participate in every cohort. For each cohort, an attempt will be made to have at least 1 subject randomized to placebo per site, which will be facilitated through block randomization.

Dose titration will be incorporated to enhance tolerability to PF-06882961 (see [Section 1.3.2.3](#)). Doses and dose titration schemes in the escalation sequence may be modified or repeated as guided by emerging safety, and PK data. The size of the dose increment and titration rate may be reduced or increased as the study progresses dependent

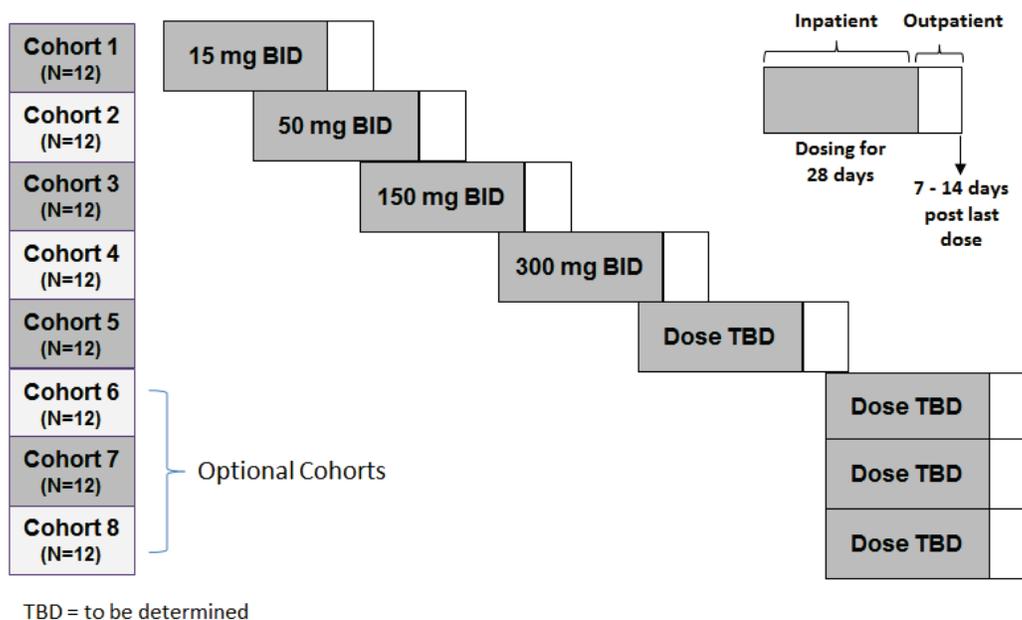
upon emerging PK, safety and tolerability data, but dose increments from one cohort to the succeeding cohort will not be greater than approximately semi-logarithmic. Doses and dosing durations for Cohort 5 and optional Cohorts 6-8 will be provided to investigators in writing prior to initiation of dosing in these cohorts. Predicted steady state exposures for all cohorts will also not exceed the proposed PK stopping limits (see [Section 1.3.2.3](#) and [Section 3.2](#)).

Subjects will be admitted to the clinical research unit (CRU) on or before Day -2 and may be discharged at PI discretion following completion of all assessments on Day 30, as described in [Table 1](#) and [Section 7](#). For individual subjects, the total duration of participation from the Screening visit to the on-site Follow-up visit will be approximately 15 weeks. A Follow-up visit and a Follow-up contact (may be a phone call) will occur 35-42 days and 56-63 days following the first dose of IP on Day 1, respectively. Subjects who discontinue prior to completion of the study may be replaced, at the discretion of the PI and Sponsor.

Dosing is anticipated to occur with food, as listed in the [Schedule of Activities](#) and [Section 4.4.1](#).

The formulations administered in this study will be PF-06882961 CCI tablets, or matching placebo (see [Section 5](#)). A Sample study design overview is shown in [Figure 1](#), however, treatment sequences, actual doses, target exposures, formulation, fasting state, titration, and dose increments may be adjusted during the study based on emerging safety, tolerability, and PK data.

Figure 1. Study Design Overview



3.2. Dose Escalation and Stopping Rules

Dose escalation and stopping rules will be used to determine whether the MTD has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the sponsor study team and the PI. The sponsor study team may not overrule the PI's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the IP.

The dose escalation will be halted based on the following criteria:

- If 50% or more of the subjects receiving active drug at a given dose level (but not subjects receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities, or severe AEs in the same organ class, indicating dose-limiting intolerance.
- Dosing will be paused for any serious adverse event (SAE) that occurs in a subject receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug-related by the PI and sponsor. If the SAE is determined to be either drug-related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to subjects with the resumption of dosing will be implemented. Such a plan could include measures such as a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.
- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigators.
- Other findings that, at the discretion of the study team and the investigators, indicate that dose escalation should be halted.
- If, at any dose level, the average exposure reaches or exceeds the PK stopping limits:
 - C_{\max} : 26177 ng/mL total (ie, 767 ng/mL unbound) or
 - AUC_{24} : 199860 ng·h/mL total (ie, 5856 ng·h/mL unbound).
- If, based on the observed data, the group mean C_{\max} or AUC (based on total plasma concentration) of the next planned dose is projected to exceed the escalation limits, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

Progression to the next cohort dose level will occur if the prior dose was determined to be sufficiently tolerated and after satisfactory review of the available safety and PK data. Data required for dose escalation evaluation will be determined by cohort:

- For Cohorts 1 and 2: dose escalation will be based on review of safety and PK data through Day 14 (as listed in [Table 1](#) and [Table 2](#) in the [Schedule of Activities](#)).
- For Cohorts 3 and 4: Dose escalation will be based on review of safety data and PK through Day 21 (as listed in [Table 1](#) and [Table 2](#) in the [Schedule of Activities](#)).
- For Cohort 5 and optional Cohorts 6, 7 and 8 (if evaluated): timing of safety and PK data will be determined based on dosing paradigm for that cohort, and will be either Day 14 safety and PK or Day 21 safety and PK (as listed in [Table 1](#) and [Table 2](#) in the [Schedule of Activities](#)). The timing of safety and PK required for dose escalation for these cohorts will be provided in writing prior to initiation of dosing for these cohorts.
- For all study cohorts, each dose escalation will be based on review of available safety and PK data for at least 8 subjects (including at least 1 placebo) from that cohort.

Details on safety assessments included in dose escalation review are provided in [Section 7.1](#) and [Table 1](#).

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Patients with T2DM who are taking metformin monotherapy as their only anti-hyperglycemic treatment. Metformin dose must be ≥ 500 mg per day and must be stable, defined as no change in the treatment, including dose, for at least 2 months prior to the screening visit. For further information, see [Section 5.8](#).
2. HbA1c $\geq 7.0\%$ and $\leq 10.5\%$ at screening.
3. Body mass index (BMI) of 24.5 to 45.4 kg/m²; and a total body weight > 50 kg (110 lb).
4. Males and female subjects of non-childbearing potential between the ages of 18 and 70 years, inclusive of age at the time of the screening visit.

Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

- a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
- b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- c. Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

5. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject has been informed of all pertinent aspects of the study.
6. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).
 - Patients who have chronic conditions other than T2DM (for example, hypercholesterolemia or hypertension) but are controlled by either diet or stable doses of medications may be included (for example, a subject with hypercholesterolemia on appropriate treatment is eligible). See [Section 5.8](#) for further information on concomitant medications.
2. Subjects with **any** of the following medical conditions:
 - Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, or any area of intestinal resection, active inflammatory bowel disease or pancreatic insufficiency);
 - Diagnosis of type 1 diabetes mellitus or secondary forms of diabetes;
 - 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;

- Any malignancy not considered cured (except basal cell carcinoma and squamous cell carcinoma of the skin); a subject is considered cured if there has been no evidence of cancer recurrence in the previous 5 years;
 - History of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb), or hepatitis C antibody (HCVAb);
 - Personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2), or subjects with suspected MTC per the PI's judgement;
 - Acute pancreatitis or history of chronic pancreatitis;
 - Acute gallbladder disease.
3. At Screening, subjects with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² as calculated by the modification of diet in renal disease equation (MDRD), and confirmed via a single repeat, if deemed necessary.
 4. A positive urine drug test. Subjects that have been medically prescribed benzodiazepines and report the use of these drugs to the investigator at the screening visit may be allowed to participate if approved by the sponsor.
 5. History of regular alcohol consumption exceeding 7 drinks/week for female subjects or 14 drinks/week for male subjects (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.
 6. Administration of an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of IP (whichever is longer).
 7. Screening supine BP ≥ 160 mmHg (systolic) or ≥ 100 mmHg (diastolic), following at least 5 minutes of supine rest. If BP is ≥ 160 mmHg (systolic) or ≥ 100 mmHg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the subject's eligibility.
 8. Screening supine 12-lead ECG demonstrating a corrected QT (QTcF) interval >450 msec or a QRS interval >120 msec. 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 subject's eligibility.
 9. Subjects with **ANY** of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

- Aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level $\geq 1.5 \times$ upper limit of normal (ULN);
 - Total bilirubin level $\geq 1.5 \times$ ULN;
 - Fasting C-peptide < 0.8 ng/mL;
 - TSH $>$ ULN;
 - Serum calcitonin $>$ ULN;
 - Amylase $>$ ULN **or** lipase $>$ ULN;
 - Blood glucose > 270 mg/dL.
10. Fasting fingerstick blood glucose (FSBG) on Day -2 of > 270 mg/dL.
11. Fertile male subjects who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for the duration of the study and for at least 28 days after the last dose of IP.
12. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
13. History of sensitivity to heparin or heparin-induced thrombocytopenia ***only if*** heparin is used to flush IV catheters.
14. Unwilling or unable to comply with the criteria in the [Lifestyle Requirements](#) section of this protocol.
15. Subjects who are 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 subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
16. 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 subject inappropriate for entry into this study.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria outlined in [Section 4.1](#) and [Section 4.2](#). The randomization ratio within a cohort will be 3:1 between PF-06882961 and placebo.

4.4. Lifestyle Requirements

The following guidelines are provided:

4.4.1. Meals and Dietary Restrictions

- ≥4-hour fast (except water) prior to admission to CRU on Day -2.
- Subjects must abstain from all food and drink (except water) at least 8 hours prior to the collection of the first blood sample at Screening, each inpatient study day, and the follow-up visit (eg, safety laboratory, PK, or PD assessment).
- Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices - see below) may be consumed with meals and the evening snack.
- The initial caloric intake/menu assigned to each subject will be based on the Harris Benedict formula (sedentary lifestyle; to be provided to the site prior to study start) using the subject's body weight measured at screening.
- On days with MMTT as listed in [Table 2](#) of the [Schedule of Activities](#) (including evening prior to MMTT) **only**: subjects will be required to consume all provided food, including the liquid meal and all standard meals provided on these days. In addition, the approximate percentage of food consumed should be recorded in the case report form (CRF).
 - Subjects will not be required to consume all provided food during standard meals on other study days.
- When a meal or snack is scheduled at the same time as an ECG, the meal will be provided after the ECGs are completed.
- Breakfast will be provided at approximately 0800 hours each day:
 - A standard breakfast will be provided after dosing on all days except those when the MMTT is administered;
 - For the MMTT, the mixed meal will be provided as 16 ounces of Ensure Plus[®] and will be administered as listed in [Table 2](#) of the [Schedule of Activities](#). The entire Ensure Plus[®] meal is to be consumed within 10 minutes. (See [Section 7.3.1](#)).
- Lunch will be provided approximately 4 hours after AM dosing (approximately 1200 hours) and at approximately the same time on each non-dosing day. On days with MMTT, lunch will be provided **after** the 4-hour postdose blood collection samples for the MMTT have been completed.

- Dinner will be provided approximately 10 hours after AM dosing (approximately 1800 hours), and after dosing, and at approximately the same time on each non-dosing day.
- An evening snack may be provided at approximately 2200 hours.
 - Subjects will receive the same snack each evening prior to the MMTT the following day. Subjects will be encouraged to consume the entire evening snack.
- Meals on days with MMTT, will be standardized such that the subjects receive the same menus for all meals on these days:
 - Subjects will be encouraged to consume their entire meals on Day -1 and evening snack on Day -2;
 - If subjects do not consume their entire meal on Day -1, they will be instructed to consume the same amount of food ($\pm 10\%$) on the other days with MMTT that they ate on Day-1. If a subject consumes approximately $<90\%$ or $>110\%$ of what s/he consumed on Day -1 based on visual inspection by the site staff, the approximate percentage consumed should be noted in the CRF;
 - The start time of all meals will be captured in the CRF on days with MMTT including the Ensure Plus[®] mixed-meal provided for breakfast.
 - Subjects will be encouraged to eat all standard meals within 30 minutes on days with MMTT administration;
- Details on the meals provided to subjects, including the menu items, portion sizes and approximate calories with nutritional macronutrient (% carbohydrate, fat and protein) breakdown of the meal will be maintained in source documentation at the CRUs. This information will not be collected in the case report form, however may be submitted to the Sponsor upon request.
- Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of IP until collection of the final PK blood sample.

4.4.2. Alcohol, Caffeine, and Tobacco

- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample. Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Caffeine containing products, up to two 8-ounce cups of coffee or its equivalent per day, will be permitted except at times outlined below.

- Caffeine containing products may not be consumed within 2 hours prior to measuring vital signs and ECGs, and may not be consumed on days with MMTT;
- Subjects may use tobacco- or nicotine-containing products during the study during scheduled smoking breaks, as permitted by the CRU practices except as noted below.
- Smoking will not be permitted during frequent sampling procedures (eg, will not be permitted until after the MMTT procedures), and will not be permitted within 2 hours prior to any vital sign and ECG assessments. Smoking will also not be permitted 2 hours before and 2 hours following any dose of PF-06882961/placebo.

4.4.3. Activity

- Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

4.4.4. Contraception

All fertile male subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of IP. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the [Schedule of Activities](#), the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects 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 subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the postvasectomy ejaculate.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of IP and continuing for at least 28 days after the last dose of IP.

4.5. 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 portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study 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 subject'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. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, IP is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the IP is PF-06882961 and its matching placebo, both administered as oral tablets.

5.1. Allocation to Treatment

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) system. 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 subject number. The site personnel will then be provided with a treatment assignment and randomization number. The IRT system will provide a confirmation report containing the subject number and randomization number assigned. The confirmation report must be stored in the site's files. Subjects will receive the blinded IP (PF-06882961 or matching placebo) corresponding to their assigned randomization number.

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

5.2. Breaking the Blind

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be a manual process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

Blood specimens will be obtained from all subjects for PK analysis to maintain the study blind at the investigator site. Specimens from subjects randomized to placebo will not be routinely analyzed. Investigator site staff [*with the exception* of the site pharmacist(s) and pharmacy assistant(s)] and blinded study monitor, if assigned, will be blinded to study treatment (PF-06882961 or placebo). Other specified Pfizer personnel, *including the separate unblinded monitor(s) (if assigned)*, will be unblinded to subject treatments in order to permit real-time interpretation of the safety and PK data; and provide information necessary to potentially alter the dose-escalation sequence. The blinded study monitor will remain blinded to treatment until all monitoring for the study has been completed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

5.3. Subject Compliance

IP will be administered under the supervision of investigator site personnel. The oral cavity of each subject will be examined following dosing to ensure the IP was taken.

5.4. Investigational Product Supplies

5.4.1. Dosage Form and Packaging

PF-06882961 will be supplied as 1 mg, 10 mg, and 100 mg IR or 50 mg  tablets for oral administration. Matching placebo tablets will also be provided. PF-06882961 or placebo tablets will be subsequently provided to the subjects in individual dosing containers according to their assigned treatment. Multiple tablets may be required to deliver the total dose.

Subjects will continue taking their own metformin medication brought from home (or provided by the site, if necessary) at the same dose and frequency that was prescribed prior to entry into the study.

5.4.2. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject/caregiver by qualified staff. Dispensing is defined as the provision of IP, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, subject, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

PF-06882961 and placebo tablets will be dispensed at the CRU by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements. The IP will be administered in a blinded fashion to the subject.

5.5. Administration

5.5.1. Administration of Blinded IP

Administration of blinded IP for all dosing regimens will occur under the conditions described in [Section 4.4.1](#).

Subjects will swallow the IP whole, without manipulating or chewing the IP prior to swallowing.

5.5.2. Administration of Metformin and Other Concomitant Medications

On all study days while in the CRU, subjects will also be given their morning dose of metformin, brought from home, at the same time as their blinded IP. For subjects taking metformin more frequently than once a day, the investigator will determine the appropriate times during the day to administer those doses, however the timing should be the same between inpatient days, and care should be exerted to minimize changes to the subject's stable medication routine. Some flexibility around dosing times of concomitant medications is allowed (see [Section 5.8](#)), but as much as possible, subjects should maintain a similar

dosing schedule for all concomitant medications, including metformin, as they did prior to the study.

5.6. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all IPs are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

IPs should be stored in their original containers and in accordance with the labels.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product-label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the IP must be quarantined and not used until Pfizer provides permission to use the IP. It will not be considered a protocol deviation if Pfizer approves the use of the IP after the temperature excursion. Use of the IP prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP supplies. All IPs will be accounted for using a drug accountability form/record.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused IP (eg, at the site). If destruction is authorized to take place at the investigator site, the PI 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.

5.8. Concomitant Treatment(s)

Subjects in this trial will be allowed to be on certain concomitant medications that have been prescribed to treat concurrent diseases such as hyperlipidemia and hypertension. Attempts must be made **not** to alter the doses and regimens of the background medications after randomization and for the duration of participation in this study. Any changes must be captured in the CRF.

Treatments taken within 28 days before the first dose of IP will be documented as a prior treatment. Treatments taken after the first dose of IP will be documented as concomitant treatments.

Medications, prescription or non-prescription or herbal supplements not specifically listed in [Section 5.8.5](#) may be permitted, but only after review and approval by the Sponsor.

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

5.8.1. Medications for Glycemic Control

All subjects are required to be taking metformin monotherapy prior to inclusion in this study, as listed in [Section 4.1](#). At screening, this study requires that subjects have been taking a minimum metformin dose of ≥ 500 mg/day for at least 2 months prior to the screening visit. The dose of metformin, where possible, is expected to remain the same until completion of study participation (ie, Follow-up visit).

Use of other medications for glycemic control is **not permitted** in this study (see [Section 5.8.5](#)).

5.8.2. Antihypertensive Medications

The use of background antihypertensive agent(s) is permitted (unless noted in [Section 5.8.5](#)). Doses of antihypertensive agents must be stable for at least 4 weeks prior to screening and throughout the study. Changes in dosing regimen of such agents, if necessary, may be permitted after discussion with the Sponsor. These changes must be captured in the CRF.

5.8.3. Lipid-Modifying Medications

The use of background lipid-modifying agents is permitted (except as noted in [Section 5.8.5](#)). Doses of such lipid-modifying agents must be stable for at least 4 weeks prior to screening and throughout the study. Changes in dosing regimen of such agents are **not** permitted during the study.

5.8.4. Management of Nausea and Vomiting

Nausea and vomiting have been reported with administration of GLP-1R agonists. Subjects complaining of nausea may be managed conservatively with bed rest and/or fluid management at the discretion of the investigator. If the nausea and vomiting are not amenable to conservative management, anti-emetics (eg, prochlorperazine, promethazine, ondansetron) may be administered at the investigator's discretion with notification to the sponsor and entry in the CRF.

5.8.5. Prohibited Medications

5.8.5.1. Medications Not Permitted within 3 Months of Screening

The use of the following classes of agents is **not** permitted within **3 months prior to screening** and for the duration of participation in the study:

- Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone;
- Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, pramlintide).

5.8.5.2. Medications Not Permitted within 4 Weeks of Screening

In addition to the above, subjects on the following background medications must have these agents discontinued **at least 4 weeks prior to Screening**:

- Other oral anti-diabetic medications, including:
 - Sulfonylureas such as acetohexamide, chlorpropamide, tolazamide, tolbutamine, glimepiride, glipizide, glyburide;
 - Meglitinide analogues such as repaglinide, nateglinide;
 - Dipeptidyl peptidase-4 inhibitors (DPP-4i) such as sitagliptin, saxagliptin, vildagliptin;
 - α -glucosidase inhibitors such as acarbose, miglitol;
 - Sodium-glucose cotransporter-2 (SGLT2) inhibitors such as canagliflozin;
- Systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone;

- **Note:** As an exception, steroid-containing inhalers, nasal sprays and topical formulations *are permitted* in this study;
- Immunosuppressants such as cyclosporine and tacrolimus;
- Appetite- or weight-modifying medications, including non-prescription or herbals;
- Pharmacological agents with approved indication for weight loss such as orlistat and sibutramine;
- (Medical-grade) marijuana, regardless of medical indication;
- Anti-psychotic medications such as olanzapine, risperidone;
- Antidepressant medications such as tricyclic agents, selective serotonin reuptake inhibitors, and serotonin/norepinephrine reuptake inhibitors;
- Coumarin-type anticoagulants or other anticoagulants (eg, dabigatran);
- Anticonvulsants;
- Opioids;
- Antiarrhythmic;
- Non-selective β -blockers;
- Thiazide diuretics >25 mg per day;
- Sympathomimetic agents;
- Rosuvastatin.

5.8.5.3. Medications Not Permitted for Doses Above 300 mg BID

As described in [Section 1.2.2](#), PF-06882961 is a reversible inhibitor of CYP2C8 and UGT1A1 and is a weak time- and NADPH-dependent inhibitor of CYP3A4/5. As such, PF-06882961 at doses where projected AUC₂₄ exposure is expected to exceed approximately 7392 ng.h/mL should not be administered with drugs that are primarily metabolized by these enzymes.

Based on preliminary modeling of PK data emerging from the ongoing FIH study, this AUC₂₄ is currently predicted to be achieved at PF-06882961 doses exceeding 300 mg BID ([Table 4](#)). Therefore, for cohorts administered doses of PF-06882961 above 300 mg BID only (this dose level may be refined based on emerging data from this study), subjects on a background therapy (for example, for treatment of hypertension or dyslipidemia) which is known to have a high risk of DDI through CYP3A, CYP2C8 or

UGT1A1, must switch to another acceptable treatment, as determined by the subject's physician or the PI, ***at least 4 weeks prior to Day 1*** (a non-exhaustive list of such medications is provided in [Appendix 2](#)). In addition, subjects must be in a stable condition, conforming to all Inclusion/Exclusion criteria (see [Section 4.1](#) and [Section 4.2](#)).

5.9. Rescue Medication

There is no rescue therapy to reverse any AEs observed with administration of IP; standard medical supportive care must be provided to manage the AEs (see [Section 5.8.4](#) for management of nausea and vomiting).

For medical management of hypoglycemia, the investigator may administer oral carbohydrate, glucagon, or IV glucose according to his or her medical judgment. At a minimum however, treatment or administration of a scheduled meal should be given if glucose falls <60 mg/dL for at least 15 minutes, irrespective of whether the subject exhibits symptoms. Investigators may choose to administer treatment sooner if subjects have bothersome symptoms of hypoglycemia along with glucose values of ≤ 70 mg/dL.

No rescue therapy will be provided for hyperglycemia. If a subject has sustained elevated fasting plasma glucose concentrations that are >270 mg/dL on 3 consecutive measurements over 3 days, that subject will be discontinued, and the investigator will recommend further appropriate glycemic treatment according to the local healthcare standards and national guidelines.

6. STUDY PROCEDURES

6.1. Proposed Chronology of Procedures

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, ***where possible***.

- *ECGs*: obtain prior to vital sign measurements and as close as possible to the scheduled time, but prior to blood specimen collection (refer to [Section 7.1.5](#));
- *Vital Signs (BP and pulse rate)*: obtain as close as possible to the scheduled time, but prior to blood specimen collection (refer to [Section 7.1.4](#));
- *Fasting blood samples*: after assessment of 12-lead ECG and vital signs but prior to dosing;
- *PK blood specimens*: obtain at the scheduled time (refer to [Section 7.2.1](#));
- *Other pre-dose procedures*: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection;
- *Dosing*: must occur at the scheduled nominal time (refer to [Section 5.5](#)) and following predose blood sample collection.

- ***If*** an IV catheter is placed for serial blood sample collections, ECGs and vital signs (pulse rate, BP) assessments should be either collected prior to the insertion of the catheter or sufficient rest period after catheter insertion introduced to minimize impact of catheter placement on these assessments.

6.2. Screening

Refer to the [Schedule of Activities](#) for the study procedures to be completed at the screening visit. A signed and dated ICD will be obtained from each subject at the screening visit before performing any protocol-specific procedures.

Subjects will be screened within 28 days prior to administration of the blinded IP to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in [Section 1.2.3](#).

A subject who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group for this study. Subjects may be re-screened and all screening procedures must be repeated and the subject assigned a new 8-digit study-specific subject identification number (SSID) number. This criterion would also apply to subjects who screened for this study more than 28 days prior to dosing.

To prepare for study participation, subjects will be instructed on the information in [Section 4.4](#) and [Section 5.8](#) of the protocol.

6.3. Study Period

Refer to the [Schedule of Activities](#) for the study procedures to be completed during the Study Period.

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If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the CRU and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.4. Follow-up

6.4.1. Follow-up Visit

Subjects will return to the CRU 7 to 14 days following the last dose of IP for a Follow-up visit. Refer to the [Schedule of Activities Table 1](#) and [Table 2](#) for the study procedures to be completed at this visit.

6.4.2. Follow-up Contact

Follow-up contact will be completed at least 28 calendar days and up to 35 calendar days after the last administration of the investigational product to capture any potential AEs (see [Section 8.1.4](#)) and to confirm appropriate contraception usage (see [Section 4.4.4](#)). Contact with the subject may be done via a phone call.

6.5. Subject Withdrawal/Early Termination

Withdrawal of consent:

Subjects 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 subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects 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 investigational product 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 subject 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.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also [Section 8.1.3](#)) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given investigator site. The early termination visit applies only to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject twice. After 2 attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early-withdrawal visit, every effort must be made to complete the following assessments:

- Full physical examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit;
- Supine BP and pulse rate measurements;
- 12-Lead ECG measurement;
- Blood and urine specimens for safety laboratory tests;
- Blood sample for PK analysis.

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

If the subject withdraws from the study and also withdraws consent 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.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor provided that the nature of the safety event does not preclude dose escalation and that exposure stopping limits are observed.

7. ASSESSMENTS

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 subject. 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.

7.1. Safety

7.1.1. Laboratory Tests

The following clinical laboratory tests will be performed at times defined in the [Schedule of Activities](#) 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 7. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea	pH	FSH ^b
Hematocrit	Creatinine	Glucose (qual)	Urine drug screening
RBC count	Plasma glucose (fasting)	Protein (qual)	HIV ^c
MCV	Calcium	Blood (qual)	HepBsAg ^c
MCH	Sodium	Ketones	HepBcAb ^c
MCHC	Potassium	Nitrites	HCVAb ^c
Platelet count	Chloride	Leukocyte esterase	HbA1c
WBC count	Total CO ₂ (bicarbonate)	Urobilinogen	C-peptide ^d
Total neutrophils (Abs)	AST	Urine bilirubin	
Eosinophils (Abs)	ALT	Microscopy ^a	
Monocytes (Abs)	Total bilirubin		
Basophils (Abs)	Alkaline phosphatase		
Lymphocytes (Abs)	Uric acid		
PT/INR/aPTT	Albumin		
	Total protein		
	Serum total bile acids ^d		
	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 female subjects to confirm post-menopausal status only; at screening.
- c. At Screening only.
- d. Assessed at Screening for exclusion, but also as part of MMTT.

- The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.
- In addition to the clinical laboratory tests listed in Table 7, blood samples will be drawn and analyzed for calcitonin, amylase, lipase, lipid panel, TSH and FT4 at the time points listed in Table 1 and Table 2 in the Schedule of Activities. Review of these data is not required prior to dose escalation in each cohort, cumulative results will be reviewed as they become available.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the clinical study report (CSR). Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

7.1.2. Physical Examinations

Physical examinations should be performed at nominal time points specified in the [Schedule of Activities](#) of this protocol.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

7.1.3. Body Weight

Body weight measurements will be obtained at the time points outlined in the [Schedule of Activities](#). If possible, the same scale should be used for a particular subject for all body weight measurements obtained at the CRU. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface.

Body weight will be measured at outpatient visits to the study site as listed in [Table 1](#) of the [Schedule of Activities](#) under the following conditions:

- After void of urine;
- After removal of shoes, bulky layers of clothing, and jackets so that only light clothing remains;
- While remaining still during measurement.

During admission to the CRU, body weight will be measured at the time points listed in [Table 2](#) of the [Schedule of Activities](#). Measurement will be taken under the following conditions:

- In the morning, prior to eating and drinking;
- After the subject has been asked to void;
- While wearing only a hospital gown and no shoes;
- While remaining still during measurement.

7.1.4. Blood Pressure and Pulse Rate

BP and pulse rate will be measured at times specified in the [Schedule of Activities](#) section of this protocol. 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.

Supine BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Subjects should be instructed not to speak during measurements. When triplicate BP and pulse rate are required, they will be obtained approximately 2 to 4 minutes apart; the average of the triplicate BP and pulse rate measurements collected at each nominal time point on Day -1 will serve as each subject's time-controlled baseline values.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection (refer to [Section 6.1](#)).

7.1.5. Electrocardiogram

12-Lead ECGs should be collected at times specified in the [Schedule of Activities](#) section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position. When a meal or snack is scheduled at the same time as an ECG, the ECG must be performed prior to the meal/snack.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected at each nominal time point on Day -1 will serve as each subject's time-controlled baseline QTcF value.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements.

If the QTcF interval is increased by ≥ 45 msec from the baseline, or an absolute QTcF value is ≥ 500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2 to 4 minutes apart, to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (ie, is ≥ 45 msec from the baseline, or is ≥ 500 msec), then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

Further ECG monitoring will occur if a) the mean value from the triplicate measurements for any post-dose QTcF interval is increased by ≥ 30 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥ 500 msec for any scheduled ECG. If either of these conditions occurs, then single ECG measurements must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTcF values remain ≥ 500 msec (or ≥ 30 msec from the baseline **and** >450 msec) for greater than 4 hours (or sooner, at the discretion of the investigator), or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner, at the discretion of the investigator).

ECG data will be submitted to a central laboratory for overread measurement of ECG intervals and overall interpretation. The central ECG laboratory will be blinded to treatment allocation. The final ECG report from the central laboratory should be maintained in the subject's source documentation and be the final interpretation of the ECG recording.

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

7.1.6. Glucometer Monitoring of Glucose

Investigators will monitor FSBG using glucometer measurements at the times specified in the [Schedule of Activities](#). FSBG measurements should be taken before breakfast while the subject is confined to the CRU.

FSBG readings will be maintained at the sites in source documents, and only the glucose results from the laboratory will be reported in the study database. The sites may share the FSBG readings with the Sponsor for the purpose of dose-escalation decisions, but these data will be stored in the sites' source documents unless related to an AE as described below.

Specifically, if an FSBG result is ≤ 70 mg/dL, a second FSBG should be obtained to confirm the glucose value, in addition to a venous sample that will be sent to the clinical laboratory for confirmation. If the value from this second FSBG is also ≤ 70 mg/dL, the second value will be recorded as a hypoglycemic AE. FSBG will continue to be monitored until the glucose value returns to >70 mg/dL. Samples may be taken more frequently if deemed necessary by the investigator. FSBG readings from a glucometer are permitted at any time if the investigator or subject notes symptoms of hypoglycemia.

7.1.7. Hypoglycemia Reporting

Hypoglycemia will be assessed and reported in several categories: severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, and probable hypoglycemia.

Severe hypoglycemia: In order to be considered severe hypoglycemia all of the following criteria must be met:

- The subject required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- The subject exhibited at least one of the following neurological symptoms:
 - Memory loss;
 - Uncontrollable behavior;
 - Irrational behavior;
 - Unusual difficulty in awakening;
 - Suspected seizure;
 - Seizure;
 - Loss of consciousness.
- The subject had one of the following:
 - Blood glucose <50 mg/dL, or
 - If blood glucose was not measured, the clinical manifestations were reversed by carbohydrate administration.

Documented symptomatic hypoglycemia: An event during which typical symptoms of hypoglycemia are accompanied by a measured glucose concentration ≤ 70 mg/dL.

Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured glucose concentration ≤ 70 mg/dL.

Probable symptomatic hypoglycemia: An event, during which typical symptoms of hypoglycemia are not accompanied by a “real time” glucose determination, but were presumably caused by a plasma glucose concentration ≤ 70 mg/dL. The clinical picture must include prompt resolution with oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

7.2. Pharmacokinetics

7.2.1. Plasma for Analysis of PF-06882961

During all study periods, sufficient volume of blood (approximately 3 mL) to provide a minimum of approximately 1 mL plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K₂EDTA) at times specified in the [Schedule of Activities](#) section of the protocol.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. For samples up to and including 10 hours post-dose, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF). For samples more than 10 hours post-dose, samples obtained ≤1 hour away from the nominal time post dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF).

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

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site 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.

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 will not be included in the CSR.

7.2.2. Urine for Analysis of PF-06882961 and/or Metabolite Screening

Urine will be collected at times specified in the [Schedule of Activities](#).

- ***Prior to dosing on Day 1***, each subject must complete a forced void with an **aliquot** (approximately 10 mL) from this urine (urine blank) labeled and stored frozen for measurement of drug concentrations, per detailed instructions offered in a laboratory manual prior to the start of the study.
- ***Following dosing on Day 28***, each void post dose will be collected and saved in a container and stored in refrigerated conditions (ie, 2-8°C) for the duration of the collection interval, as specified in [Table 2](#) of the [Schedule of Activities](#).

- At the end of the collection interval, subjects must complete a forced void with this complete void included as part of the interval collection;
- The urine container will be mixed thoroughly and total volume plus weight of the urine collected during the interval recorded;
- An **aliquot** (approximately 20 mL) will be labeled and stored frozen for the potential measurement of drug concentrations and for potential metabolite screening per detailed instructions offered in a laboratory manual prior to the start of the study; and the remaining urine discarded.

Details regarding the processing, storage and shipping of the samples will be provided in the lab manual. The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study. The urine samples must be processed as indicated to maintain sample integrity. Any deviations from the urine sample processing steps given in the protocol or lab manual, 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 sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation. Samples for analysis of PF-06882961 PK will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Metabolite screening may be conducted at selected dose(s) first; based on these results a decision on whether or not to analyze samples from remaining doses may be made. As part of understanding the properties of the study drug, urine samples may be used for evaluation of the bioanalytical method as well as for other internal exploratory purposes. These data would be used for internal exploratory purposes and would not be included in the CSR.

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7.5. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 550 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. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety 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) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the [Serious Adverse Events](#) section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the [Subject Withdrawal](#) section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the [Requirements](#) section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each subject begins from the time the subject provides informed consent, which is obtained before the subject’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject 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 investigational product must be reported to Pfizer Safety.

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.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease (omit for oncology and anti-retroviral studies);
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);

- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (\times 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 ($>2 \times$ ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above $3 \times$ ULN (ie, AST/ALT and TBili values will be elevated within the same lab 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 subject's individual baseline values and underlying conditions. Subjects 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:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times \text{ULN}$ AND a TBili value $>2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $<2 \times \text{ULN}$ or not available.
- For subjects 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 $>3 \times \text{ULN}$; or $>8 \times \text{ULN}$ (whichever is smaller).
 - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ **or** if the value reaches $>3 \times \text{ULN}$ (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 subject 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, 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, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. 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) 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 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.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.2.1. Exposure During Pregnancy

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 investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
- 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 investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, 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 subject 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 pre-procedure 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 investigational product.

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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. 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.

8.4.2.3. 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 subject 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.

8.4.3. Medication Errors

Other exposures to the investigational product 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

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

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 immediately.

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 non-serious, 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**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a 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. Sample Size Determination

A sample size of up to approximately 12 subjects per cohort (9 active, 3 placebo) has been selected to minimize exposure to humans to a new chemical entity while allowing adequate characterization of safety and tolerability, PK, and PD at each dose level.

9.2. Efficacy Analysis

Efficacy analysis is not applicable to this study.

9.3. Pharmacokinetic Analysis

The PK concentration population will be defined as all randomized subjects who received at least 1 dose of PF-06882961 and in whom at least 1 plasma PK concentration value is reported. The PK parameter analysis population will be defined as all randomized subjects who received at least 1 dose of PF-06882961 and who have at least 1 of the PK parameters of interest calculated. PK samples from placebo samples will not be routinely analyzed.

Analysis and reporting of preliminary, qualitative characterization of metabolite profile of PF-06882961 using pooled plasma and urine samples, if performed, will be reported separately (and not included in the CSR).

9.3.1. Derivation of Pharmacokinetic Parameters

The PK parameters for PF-06882961 following Day 1 and multiple dose administration will be derived from the concentration-time profiles, as data permit. The PK parameters to be assessed in this study, their definition and method of determination are outlined in [Table 8](#), [Table 9](#) and [Table 10](#). Actual PK sampling times will be used in the derivation of PK parameters. R_{ac} parameters will be calculated for titration cohorts after appropriate dose normalization. Additional detail on PK parameter definition for titrated and non-titrated cohorts will be provided in the SAP.

Table 8. Definition of Plasma PK Parameters for PF-06882961 in the Setting of BID Dosing

Parameter	Day 1 (D1) or Steady State (SS)	Definition	Method of Determination
C_{max1} and C_{max2}	D1 & SS	C_{max1} : maximum plasma concentration during the dosing interval $\tau_1=0$ to 10 hours C_{max2} : maximum plasma concentration during the dosing interval $\tau_2=10$ to 24 hours	Observed directly from data
C_{max}	D1 & SS	Maximum plasma concentration observed from time zero to 24 hours	Observed directly from data
T_{max} , T_{max1} and T_{max2}	D1 & SS	Time for C_{max} , C_{max1} and C_{max2}	Observed directly from data as time of first occurrence
C_{max1} (dn), C_{max2} (dn) and C_{max} (dn)	D1 & SS	C_{max1} , C_{max2} and C_{max} normalized to a 1 mg dose.	$C_{max1}/Dose$ $C_{max2}/Dose$ $C_{max}/Dose$
AUC_{τ_1} and AUC_{τ_2}	D1 & SS	Area under the plasma concentration-time profile from time zero to time τ , where $\tau_1 = 0$ to 10 hours and $\tau_2=10$ to 24 hours k	Linear/Log trapezoidal method
AUC_{τ_1} (dn) and AUC_{τ_2} (dn)	D1 & SS	AUC_{τ_1} and AUC_{τ_2} normalized to a 1 mg dose.	$AUC_{\tau_1}/Dose$ $AUC_{\tau_2}/Dose$
AUC_{24}	D1 & SS	Area under the plasma concentration-time profile from time zero to time 24 hours	$AUC_{\tau_1} + AUC_{\tau_2}$
AUC_{24} (dn)	D1 & SS	AUC_{24} normalized to a 1 mg dose.	$AUC_{24}/Dose$
AUC_{last}	SS	Area under the plasma concentration-time profile from time zero to time of last quantifiable concentration	Linear/Log trapezoidal method
AUC_{inf}	SS	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}^*/k_{el})$, where C_{last}^* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis and k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.

AUC _{inf} (dn)	SS	AUC _{inf} normalized to a 1 mg dose	AUC _{inf} /Dose
CL/F	SS	Apparent clearance over 24 hours	Dose/AUC ₂₄
C _{min}	SS	Minimum plasma concentration during the interval 0 to 24 hours.	Observed directly from data
C _{av}	SS	Average plasma concentration over 24 hours.	AUC ₂₄ /24
R _{ac}	SS	Observed accumulation ratio for AUC ₂₄	Non-titrated cohort(s): Steady State AUC ₂₄ / Day 1 AUC ₂₄ Titrated cohorts: R _{ac} parameters will be calculated after appropriate dose normalization
R _{ac,Cmax1} R _{ac,Cmax2} and R _{ac,Cmax}	SS	Observed accumulation ratio for C _{max}	Non-titrated cohort(s): Steady State C _{max1} / Day 1 C _{max1} Steady State C _{max2} / Day 1 C _{max2} and Steady State C _{max} / Day 1 C _{max} Titrated cohorts: R _{ac} parameters will be calculated after appropriate dose normalization
PTR	SS	Peak-to-trough ratio	C _{max} /C _{min}
t _{1/2}	SS	Terminal half-life	Log _e (2)/k _{el} , where k _{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
V _z /F	SS	Apparent volume of distribution	Dose/(AUC ₂₄ * k _{el})

Table 9. Definition of Plasma PK Parameters for PF-06882961 in the Setting of QD Dosing			
Parameter	Day 1 or Steady State (SS)	Definition	Method of Determination
C_{max}	D1 & SS	Maximum plasma concentration observed from time zero to 24 hours	Observed directly from data
T_{max}	D1 & SS	Time for C_{max}	Observed directly from data as time of first occurrence
C_{max} (dn)	D1 & SS	C_{max} normalized to a 1 mg dose.	$C_{max}/Dose$
AUC_{24}	D1 & SS	Area under the plasma concentration-time profile from time zero to time 24 hours	Linear/Log trapezoidal method
AUC_{24} (dn)	D1 & SS	AUC_{24} normalized to a 1 mg dose.	$AUC_{24}/Dose$
AUC_{last}	SS	Area under the plasma concentration-time profile from time zero to time of last quantifiable concentration	Linear/Log trapezoidal method
AUC_{inf}	SS	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}^*/k_{el})$, where C_{last}^* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis and k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression..
AUC_{inf} (dn)	SS	AUC_{inf} normalized to a 1 mg dose	$AUC_{inf}/Dose$
CL/F	SS	Apparent clearance	$Dose/AUC_{24}$
C_{min}	SS	Minimum plasma concentration during the interval 0 to 24 hours.	Observed directly from data
C_{av}	SS	Average plasma concentration over 24 hours.	$AUC_{24}/24$
R_{ac}	SS	Observed accumulation ratio for AUC_{24}	Non-titrated cohort(s): Steady State $AUC_{24}/Day 1 AUC_{24}$ Titrated cohorts: R_{ac} parameters will be

$R_{ac,C_{max}}$	SS	Observed accumulation ratio for C_{max}	calculated after appropriate dose normalization Non-titrated cohort(s): Steady State $C_{max} / \text{Day } 1 C_{max}$ Titrated cohorts: R_{ac} parameters will be calculated after appropriate dose normalization
PTR	SS	Peak-to-trough ratio	C_{max}/C_{min}
$t_{1/2}$	SS	Terminal half-life	$\text{Log}_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
V_z/F	SS	Apparent volume of distribution	$\text{Dose}/(\text{AUC}_{24} * k_{el})$

Table 10. Definition of Urine PK Parameters for PF-06882961

Parameter	Steady State (SS)	Definition	Method of Determination
Ae_{24}	SS	Amount of unchanged drug recovered in urine over 24 hours	Sum of [urine concentration * sample volume ^a] for each collection over the dosing interval
$Ae_{24} \%$	SS	Percent of dose recovered in urine as unchanged drug	$100 * Ae_{24}/\text{Dose}$
CL_r	SS	Renal clearance	Ae_{24}/AUC_{24}

^asample volume = (Urine weight in g / 1.020), where 1.020 g/mL is the approximate specific gravity of urine.

9.3.2. Statistical Methods for PK Data

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

Plasma concentration of PF-06882961 will be descriptively summarized and plotted by treatment, day and nominal PK sampling time. Individual subject mean and median profiles of the plasma concentration-time data will be plotted by dose and day using actual and nominal times, respectively. Mean and median profiles will be presented on both linear-linear and log-linear scales.

The plasma and urine PK parameters will be summarized descriptively by treatment and day, as appropriate. Dose normalized (to 1 mg) parameters (as listed in [Table 8](#)) may be plotted against dose (using a logarithmic scale) for each day, and will include individual subject values and the geometric means for each dose. Attainment of steady state will be assessed by a plot of predose concentrations over time.

The observed accumulation ratio for AUC_{24} and C_{max} (as listed in [Table 8](#)) will be summarized descriptively by treatment. It will be analyzed after natural log transformation using a one-way analysis of variance with a single term for treatment. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation for each treatment.

CCI [REDACTED]

[REDACTED]

[REDACTED]

CCI [REDACTED]

[REDACTED]

CCI

9.7. Safety Analysis

All subjects who received at least 1 dose of study medication will be included in the safety analyses and listings. AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported. In addition, C-peptide and HbA1c screening data will be collected and reported as demographic data.

9.7.1. Electrocardiogram Analysis

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS interval will be summarized by treatment and time.

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

Safety QTcF Assessment			
Prolongation	Mild	Moderate	Severe
Absolute value (msec)	≥450 - <480	≥480 - <500	≥500
Increase from baseline in QTcF (msec)		30 - <60	≥60

In addition, the number of subjects with corrected and uncorrected QT values >500 msec will be summarized.

At the nominal time points, the mean of the triplicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the >500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of subject factors (covariates) on the relationship will be examined. The results of such analyses will not be included in the CSR.

9.7.2. Vital Sign Analysis

Supine blood pressures and pulse will be recorded at each assessment time indicated in the [Schedule of Activities](#). The average of any triplicate measurements will be calculated prior to analyzing the data.

The maximum decrease/increase in blood pressures and pulse rate from time-matched baseline (Day -1) over all measurements taken post-dose, will be determined for each subject.

No formal inferential statistics will be applied to the vital signs data.

Actual values and changes from time-matched baseline in supine systolic and diastolic and pulse rate will be summarized by treatment, time postdose and day.

The supine systolic and diastolic BP and pulse rate measurements obtained following the Day 1 dose will have their corresponding Day 1 predose value subtracted from them. These values will then be compared with their corresponding values on Day-1, ie, the change in the time-matched Day -1 value from the baseline measure on that day. The differences will be summarized (N, mean, 90% CI) for each dose and time point. In addition, for supine systolic and diastolic BP and pulse rate, the time matched baseline subtracted differences between each dose and placebo will be summarized (N, mean, 90% CI) for each dose, time postdose and day.

Maximum values and maximum changes from time-matched baseline for vital signs will also be summarized descriptively by treatment using categories as defined in the statistical analysis plan. Numbers and percentages of subjects meeting the categorical criteria will be provided and individual values listed in the CSR.

9.7.3. Hypoglycemia Monitoring and Reporting

The hypoglycemic AEs (obtained from site glucometer readings) will be listed in a separate table and summarized categorically.

9.8. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is a sponsor-open study, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and facilitating dose-escalation decisions. In addition, these reviews may facilitate PK/PD modeling and/or supporting clinical development.

9.9. Data Monitoring Committee

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer investigator sites, 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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The 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, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code.

The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject 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 investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. 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 investigational product, 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in the United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06882961 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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 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 Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are 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 subject 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 patients 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.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the PI of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Abbreviations

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

Abbreviation	Term
Abs	Absolute
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC ₂₄	area under the curve from time zero to 24 hours
AUC _{last}	area under the concentration-time profile from time zero to the time of the last quantifiable concentration
BBS	Biospecimen Banking System
BCRP	breast cancer resistant protein
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
C _{eff}	efficacious concentration
CFB	change from baseline
CI	confidence interval
CK	creatine kinase
cLogP	partition coefficient
CL	clearance
CL/F	apparent clearance
CL _p	plasma clearance
C _{max}	maximum observed concentration
CO ₂	carbon dioxide (bicarbonate)
CC	
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variance
CYP	cytochrome P
DCT	data collection tool

Abbreviation	Term
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DPP-4i	dipeptidyl peptidase-4 inhibitors
EC ₅₀	50% of the maximum effect concentration
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
EDTA	edetic acid (ethylenediaminetetraacetic acid)
eGFR	estimated glomerular filtration rate
EU	European Union
EudraCT	European Clinical Trials Database
F	oral bioavailability
FIH	first-in-human
FPI	fasting plasma insulin
FPG	fasting plasma glucose
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
FT4	free thyroxine
fu	fraction unbound
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
HbA1c	glycated hemoglobin
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HLM	human liver microsomes
CCI	
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product

Abbreviation	Term
IP manual	investigational product manual
CC	
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IVGTT	intravenous glucose tolerance test
IWR	interactive Web-based response
K ₂ EDTA	dipotassium ethylenediaminetetraacetic acid
K _i	binding inhibition constant
LFT	liver function test
LSLV	last subject last visit
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
CCI	
MDR	multi-drug resistance protein
MDRD	modification of diet in renal disease equation
MEN2	multiple endocrine neoplasia syndrome type 2
CCI	
MTC	medullary thyroid carcinoma
MTD	maximum tolerated dose
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	nonalcoholic fatty liver disease
NOAEL	no observed adverse effect level
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PBPK	physiologically based pharmacokinetic
PCD	primary completion date
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PGx	pharmacogenomic(s)
pH	potential of hydrogen
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
QD	daily
QTc	corrected QT interval
QTcF	QT interval corrected for heartrate using Fridericia's formula

Abbreviation	Term
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SGLT2	sodium-glucose cotransporter-2
SoC	standard of care
SOP(s)	standard operating procedure(s)
SRSD	single reference safety document
SS	steady state
SSID	study-specific subject identification number
t _{1/2}	half-life
T2DM	type 2 diabetes mellitus
TBD	to be determined
TBili	total bilirubin
THC	tetrahydrocannabinol
TK	toxicokinetic
T _{max}	time for C _{max}
TSH	thyroid stimulating hormone
TZDs	thiazolidinediones
UGT	uridine glucuronosyl transferase
ULN	upper limit of normal
US	United States
V _{ss}	distribution volume
WBC	white blood cell

Appendix 2. Concomitant Medications

Subjects on a background therapy which is known have a high risk of Drug-Drug Interaction must discontinue those treatments and be placed on alternative medication, as judged appropriate by the subject's physician or the Principal Investigator, as described in [Section 5.8](#). These medications include, but are not limited to, those indicated in the table below.

Note that only drugs used for the treatment of hypertension or dyslipidemia (common concomitant chronic diseases in T2DM patients) are listed here. Background therapies not specifically mentioned here should be assessed for potential interactions by the Principal Investigator on a case-by-case basis.

Indication	1. Excluded Medication	2. Allowable Medication
Hypertension	<p><u>Renin Inhibitors:</u> Aliskiren (<i>Texturna</i>®)</p> <p><u>Diuretics:</u> Eplerenone (<i>Inspira</i>®)</p> <p><u>Calcium Channel Blockers</u> including: Felodipine (<i>Plendil</i>®) Nifedipine (<i>Adalat</i>®, <i>Procardia</i>®) Amlodipine (<i>Norvasc</i>®) Diltiazem (<i>Cardizem</i>® LA) Nimodipine (<i>Nimotop</i>®) Verapamil (<i>Verelan</i>® PM)</p> <p><u>Alpha/Beta Adrenergic Antagonists:</u> Carvedilol (<i>Coreg</i>®)</p>	<p><u>Diuretics:</u> Bumetanide (<i>Bumex</i>®) Chlorothiazide (<i>Diuril</i>®) Furosemide (<i>Lasix</i>®) Hydrochlorothiazide (<i>Esidrix</i>®) Spironolactone (<i>Aldactone</i>®)</p> <p><u>Alpha/Beta Adrenergic Antagonists:</u> Acebutolol (<i>Sectral</i>®) Atenolol (<i>Tenormin</i>®) Betaxolol (<i>Kerlone</i>®) Bisoprolol (<i>Zebeta</i>®) Esmolol (<i>Brevibloc</i>®) Labetalol (<i>Trandate</i>®) Metoprolol (<i>Toprol-XL</i>®, <i>Lopresor</i>®) Nadolol (<i>Corgard</i>®) Nebivolol (<i>Bystolic</i>™) Pindolol (<i>Visken</i>®) Propranolol (<i>Inderal</i>®) Timolol (<i>Timoptic</i>®)</p> <p><u>Angiotensin Converting Enzyme (ACE) Inhibitors:</u> Benazepril (<i>Lotensin</i>®) Enalapril (<i>Vaseretic</i>®) Fosinopril (<i>Monopril</i>®) Lisinopril (<i>Prinivil</i>®)</p>

		erindopril (Aceon®) Ramipril (Altace®)
		<u>Angiotensin II Inhibitors – Angiotensin Receptor Blockers (ARBs):</u> Candesartan (Atacand®) Eprosartan (Teveten®) Irbesartan (Avapro®) Losartan (Cozaar®) Olmesartan (Benicar®) Telmisartan (Micardis®) Valsartan (Diovan®)
Dyslipidemia	<u>HMG CoA Reductase Inhibitors (Statins):</u> Atorvastatin (<i>Lipitor</i> ®) Lovastatin (<i>Mevacor</i> ®) Simvastatin (<i>Zocor</i> ®) Fluvastatin (<i>Lescol</i> ®) Rosuvastatin (<i>Crestor</i> ®)	<u>HMG CoA Reductase Inhibitors (Statins):</u> Pitavastatin (<i>Livalo</i> ®) Pravastatin (<i>Pravachol</i> ®)
	<u>Fibric Acid Derivatives:</u> Gemfibrozil (<i>Lopid</i> ®)	<u>Fibric Acid Derivatives:</u> Fenofibrate (<i>Tricor</i> ®)
	<u>Cholesterol Absorption Inhibitors:</u> Ezetimibe (<i>Zetia</i> ®)	