AN 8-WEEK, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED PHASE 1 STUDY TO EVALUATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND TOLERABILITY OF PF-06882961 IN CHINESE ADULTS WITH TYPE 2 DIABETES MELLITUS

Study Intervention Number:	PF-06882961
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Short Title: A Phase 1 Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of PF-06882961 in Chinese Adults with Type 2 Diabetes Mellitus

Protocol Amendment Summary of Changes Table

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of PF-06882961 in Chinese Adults with Type 2 Diabetes Mellitus

Rationale: The purpose of this study is to evaluate the PK, safety and tolerability of single and multiple oral doses of PF-06882961 in adult Chinese participants with T2DM who are receiving metformin as background antihyperglycemic medication. The study will be investigator- and participant-blind (sponsor-open), to permit a review of safety and tolerability in order to assess potential for drug-induced changes in participants with T2DM. CCI [redacted]

Objectives , Estimands, and Endpoints:

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To characterize the plasma PK of PF-06882961 following a single oral dose on Day 1 and following multiple, oral doses administered to adult Chinese participants with T2DM.	Not Applicable	• Single dose (10 mg): AUC_{24}, C_{max}. • Multiple dose (40 mg, 80 mg, 120 mg): AUC_{24}, $C_{max,ss}$.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the safety and tolerability of PF-06882961 following a single oral dose on Day 1 and following multiple, oral doses administered to adult Chinese participants with T2DM.	Not Applicable	• Vital signs, Electrocardiograms, Adverse events (e.g. hypoglycemia and hyperglycemia), Clinical safety laboratory assessments.
CCI [redacted]	[redacted]	
[redacted]	[redacted]	[redacted]

Overall Design

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled, oral dosing study of PF-06882961 in adult Chinese participants with T2DM inadequately controlled on diet, exercise and metformin background therapy.

The study includes a total of 12 visits, of which 4 are inpatient study visits at the site (V2, V5, V7, V10) and 5 are outpatient visits (V3, V4, V6, V8, V9) excluding screening to the site (V1). Following the screening period (V1) to confirm eligibility (up to 4 weeks), participants will be randomized at V2 to receive PF-06882961 (or matching placebo) for a duration of 8 weeks and complete dosing at V10. The dose of PF-06882961 will be increased following a prespecified titration scheme during visits V2 through V8 to reach the target dose, which will then be maintained through V10. The others are follow-up visits (V11 and V12). During the study, participants will take study intervention blindedly either at home, at an outpatient visit, or at the study site as an inpatient.

Number of Participants

Participants will receive oral doses of PF-06882961 or placebo in this study. Approximately 20 participants will be randomized to PF-06882961 or placebo at a 3:1 ratio (15 participants to PF-06882961 and 5 participants to placebo) such that at least 8 participants in PF-06882961 group will complete 120 mg and be evaluable for PK analysis. The study will be conducted at a single clinical site in China.

Intervention Groups and Duration

The target dose level is PF-06882961 120 mg BID (or matching placebo). Following the screening period to confirm eligibility (up to 4 weeks), the treatment period will be approximately 8 weeks, followed by an approximate 4-week follow-up. The total duration of participation in this study is approximately 12 weeks, not including the screening period. Dosing will occur with food (QD at Day 1 and BID at Days 2-56), and up to 6 weeks of the 8-week dosing duration will be used for dose titration to maximize tolerability of PF-06882961, as depicted in Figure 1. Downward titration or dosing is not permitted during the study; participants who do not tolerate the titration scheme and/or assigned dose may be required to discontinue dosing of study intervention. If a participant discontinues the study intervention, every effort should be made to contact the participant for the follow-up visits (V11 and V12).

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

In general, PF-06882961 plasma PK concentration and parameters data will be summarized descriptively for single dose and multiple doses separately; safety endpoints will be summarized by treatment group and dose levels; CCI [redacted]

PK parameters AUC_{24}, C_{max}, $C_{max,ss}$, CCI [redacted] will be summarized descriptively with n, arithmetic mean, standard deviation, coefficient of variation (CV%), geometric mean, geometric CV (%), median, minimum, and maximum. Box and whisker plot of individual and geometric mean will be presented for AUC_{24}, C_{max}, $C_{max,ss}$, CCI [redacted]

Concentration data will be listed and summarized descriptively by nominal PK sampling time and day (dose). Mean and median of the plasma concentration-time data will be plotted by day (dose) against nominal PK sampling time. Spaghetti plots of individual plasma concentration-time data will be provided by day (dose) and actual PK sampling time.

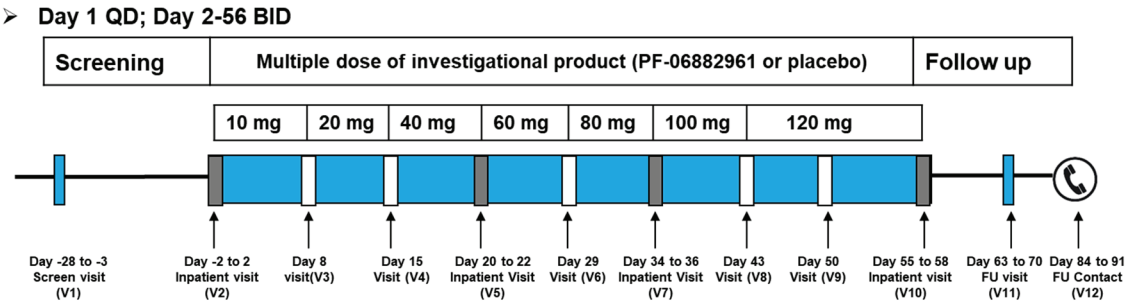
Safety data will be presented in tabular format according to the sponsor's reporting standards.

CCI

[redacted]

1.2. Schema

Figure 1. Schema of Study C3421028



1.3. Schedule of Activities

The SoA tables (Table 1 and Table 2) provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Table 1. Overall Schedule of Activities

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8	**Screen**	**Study Day (all activities at 0H [prior to AM dosing] unless otherwise specified)**																		**Follow Up**		**ET**
Visit	**V1**	**V2**				**V3**	**V4**	**V5**			**V6**	**V7**			**V8**	**V9**	**V10**				**V11**	**V12**[b]	
Weeks Relative to Dosing on Day 1		**0**				**1**	**2**	**3**			**4**	**5**			**6**	**7**	**8**				**9-10**	**12-13**	
Days Relative to Dosing on Day 1[c]	**-28 to -3**	**-2**	**-1**	**1**	**2**	**8**	**15**	**20**	**21**	**22**	**29**	**34**	**35**	**36**	**43**	**50**	**55**	**56**	**57**	**58**	**63-70**	**84 - 91**	
Informed consent & demography	x		See Table 2	See Table 2					See Table 2				See Table 2					See Table 2					
Review of eligibility criteria	x	x																					
Inpatient stay at study site		x						x				x					x		x				
Discharge from inpatient stay					x					x				x						x			
Outpatient visit (after ≥ 8-H fast)	x					x	x				x				x	x					x		
Adverse event monitoring	x	x			x	x	x	x		x	x	x		x	x	x	x		x	x	x	x	x
Medical history	x	x																					
Review prior and concomitant treatments	x	x			x	x	x	x		x	x	x		x	x	x	x		x	x	x	x	x
Review drug, alcohol, tobacco use	x	x			x	x	x	x		x	x	x		x	x	x	x		x	x	x	x	x
Review contraception use (females only)	x	x				x	x			x	x			x	x	x				x	x	x	x
Counseling on diet/exercise guidelines		x																					
Dispense glucometer and supplies, drug diary, glucose diary & provide training		x																					
Review drug diary, glucometer & glucose diary		x[d]			x	x	x	x		x	x	x		x	x	x	x				x[d]		x

Table 1. Overall Schedule of Activities

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8	**Screen**	**Study Day (all activities at 0H [prior to AM dosing] unless otherwise specified)**																		**Follow Up**		**ET**
Visit	**V1**	**V2**				**V3**	**V4**	**V5**			**V6**	**V7**			**V8**	**V9**	**V10**				**V11**	**V12**[b]	
Weeks Relative to Dosing on Day 1		**0**				**1**	**2**	**3**			**4**	**5**			**6**	**7**	**8**				**9-10**	**12-13**	
Days Relative to Dosing on Day 1[c]	**-28 to -3**	**-2**	**-1**	**1**	**2**	**8**	**15**	**20**	**21**	**22**	**29**	**34**	**35**	**36**	**43**	**50**	**55**	**56**	**57**	**58**	**63-70**	**84 - 91**	
Glucose measurement (fasting, via glucometer)		x	See Table 2	See Table 2	x	x	x	x	See Table 2	x	x	x	See Table 2	x	x	x	x	See Table 2	x	x	x		x
Physical examination (height at Screening only)	x	x																	x		x		x
Supine vital signs[e]	x					x	x			x	x			x	x	x			x		x		x
Supine 12-lead ECG[f]	x					x	x			x	x			x	x	x			x		x		x
CCI [redacted]																							
COVID-19 questionnaire[h]	x	x				x	x	x			x	x			x	x	x				x	x	x
COVID-19 pathogen by PCR[i]	x																						
Chest radiograph for COVID-19[i]	x																						
COVID-19 check temperature[j]	x	x			x	x	x	x		x	x	x		x	x	x	x		x	x	x	x	x
Dispensation of IP					x	x	x			x	x			x	x	x							
Dosing on site of IP (with meal)[k]					x	x	x	x		x	x	x		x	x	x	x						
Standardized meals/snacks[l]		x			x	x	x	x		x	x	x		x	x	x	x		x	x			
Blood Sampling for:																							
CCI [redacted]																							
Plasma C-peptide	x																						
CCI [redacted]																							
Hematology[i], chemistry (inc. eGFR)	x																				x		x
Lipids, TSH, free T4, calcitonin, amylase, lipase, serum TBA, PT/INR/aPTT	x																						x
FSH (females only)	x																						
HIV, HBsAg, HBcAb, HCVAb, Syphilis	x																						
Antibodies test of COVID-19[i]	x																						
PF-06882961 PK[m]							x				x				x				x	x			x
Urine Sampling for:																							
Urine drug test	x	x																					

Table 1. Overall Schedule of Activities

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8	Screen	Study Day (all activities at 0H [prior to AM dosing] unless otherwise specified)																		Follow Up		ET
Visit	**V1**	**V2**				**V3**	**V4**	**V5**			**V6**	**V7**			**V8**	**V9**	**V10**				**V11**	**V12[b]**	
Weeks Relative to Dosing on Day 1		**0**				**1**	**2**	**3**			**4**	**5**			**6**	**7**	**8**				**9-10**	**12-13**	
Days Relative to Dosing on Day 1[c]	**-28 to -3**	**-2**	**-1**	**1**	**2**	**8**	**15**	**20**	**21**	**22**	**29**	**34**	**35**	**36**	**43**	**50**	**55**	**56**	**57**	**58**	**63-70**	**84 - 91**	
Urinalysis (and microscopy, as appropriate)	x						x				x				x						x		x
Blood or Urine Sampling for:																							
Pregnancy test (serum) (females only) [n]	x	x				x	x				x				x	x					x		x

a. Day relative to start of study treatment (Day 1).
b. Contact may occur via telephone contact and must occur 28 to 35 days from administration of the final dose of study intervention.
c. Allowable time window for V3-V10 is ±1.
d. Review glucometer and glucose diary only.
e. Includes supine blood pressure and pulse rate; vital signs at Screening, Follow up, and early termination visit (if appropriate) are single; Triplicates vital signs should be conducted prior to AM dose at 0H on Days 8, 15, 22, 29, 36, 43, and 50. On Day 57, triplicate vital signs collected at 0H only.
f. 12-lead ECG at Screening, Follow up, and early termination visit (if appropriate) are single; Triplicate ECGs should be conducted prior to AM dose at 0H and at approximately 4H after AM dose on Days 8, 15, 22, 29, 36, 43, and 50. On Day 57, triplicate ECGs 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.
[redacted]
h. Check exposure to positive subject, residence or travel in area of high incidence and COVID-19 related signs and symptoms. To be done at least 48 hours before and at each visit.
i. An subsequent test will be performed if the participant has exposure to COVID-19 positive subject, or residence or travel in area of high incidence, or develop COVID-19 related signs and symptoms. The test may be adjusted or additional test may be required by local regulations or by the Principal Investigator.
j. To be done at least daily during residence. To be done by participant if V12 occurs via telephone contact.
k. During inpatient, both AM and PM dosing will occur at the study site, except discharge days (Days 2, 22, 36). On outpatient visit and discharge day, AM dosing will occur at the study site.
l. Meals/snacks to occur on all days while inpatient; breakfast (lunch if needed) to be provided on outpatient visits. Detailed requirements see Section 5.3.1.
m. PK samples to be collected prior to AM dose on Days 15, 29, and 43. Day 57 sample to be collected at 24H and 36H after AM dose on Day 56. Day 58 sample to be collected at 48H after AM dose on Day 56.
n. For WOCBP only: at each V2 through V10, the test result must be reviewed and deemed acceptable (ie, negative), in order to continue participation in the study.

Table 2. Schedule of Activities – Study Days -1, 1, 21, 35 & 56

[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 study site	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse event monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Review prior and concomitant treatments	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Review drug, alcohol, tobacco use	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Review drug diary, glucometer & glucose diary[b]	x													
COVID-19 check temperature	x													
Glucose measurement (fasting, via glucometer)	x													
Triplicate, supine vital sign assessment[c]	x			x		x		x		x		x		
Triplicate, supine 12-lead ECG	x			x		x		x		x		x		
CCI	[redacted]													
Randomization in trial (Day 1 only)	x													
Dosing on site of IP with meal (Days 1, 21, 35, and 56 only)	x[d]										x[e]			
Standardized meal/snack[f]	x[g]							x			x		x	
Blood Sampling for:														
CCI	[redacted]													
[redacted]	[redacted]													
Hematology, chemistry (inc. eGFR) (Days -1, 21, 35, 56 only)	x													
Lipids, TSH, free T4, calcitonin, amylase, lipase, TBA, PT/INR/aPTT (Days -1 and 56 only)	x													
PF-06882961 PK (Days 1, 21, 35, and 56 only)	x[h]			x		x		x	x	x	x	x	x	x
Urine Sampling for:														
Urinalysis (and microscopy, as appropriate) (Day -1 only)	x													
Blood or Urine Sampling for:														
Pregnancy test (for WOCBP only) (Days 21, 35, 56 only)	x													

a. On Day -1, nominal time to match approximate clock time of collection planned on Day 1 to permit time matched comparison.

b. Review glucometer and glucose diary only on Day -1.

c. Includes blood pressure and pulse rate.

d. Dosing expected to occur with breakfast or mixed meal. Day 1 only single dose at 0H

e. Dosing expected to occur with dinner. No dosing at this timepoint on Day 1.

f. Meals/snacks to occur on all days while inpatient; identical meals/snacks on Days -1, 1, 21, 35, and 56.

g. Standard breakfast on Day 1 and all other inpatient days.

h. Collection following fasting duration.

2. INTRODUCTION

GLP-1 is a neuroendocrine hormone predominantly released from the small intestine in response to food intake.[1] GLP-1 activation of the GLP-1R stimulates insulin release, inhibits glucagon secretion in a glucose-dependent manner, and delays gastric emptying.[2,3] In addition, GLP-1 has been shown to increase satiety and suppress food intake.[4] PF-06882961 is an orally administered, small molecule GLP-1R agonist that has been demonstrated, in nonclinical models, to stimulate glucose-dependent insulin release and suppress food intake with equivalent efficacy to an injectable peptide GLP-1R agonist approved for the treatment of T2DM.

PF-06882961 is an oral, small molecule GLP-1R agonist that is currently being investigated as an adjunct to diet and exercise to improve glycemic control in adult participants with T2DM.

2.1. Study Rationale

The purpose of this study is to evaluate the PK, safety and tolerability of single and multiple oral doses of PF-06882961 in adult Chinese participants with T2DM who are receiving metformin as background antihyperglycemic medication. The study will be investigator- and participant-blind (sponsor-open), to permit a review of safety and tolerability in order to assess potential for drug-induced changes in participants with T2DM. CCI [redacted]

2.2. Background

The increase in the global prevalence of T2DM is largely attributed to rising rates of excess body weight and obesity.[5] T2DM is estimated to affect more than 424 million people worldwide,[6] and Asia is a major area of the rapidly emerging T2DM global epidemic, with China and India the top 2 epicentres (109.6 and 69.2 million of adults with diabetes in 2015).[7] The latest nationally representative epidemiological survey indicated that the overall prevalence of diabetes in mainland China in 2017 was 12.8% using the ADA diagnostic criteria and 11.2% using World Health Organization criteria. There are about 130 million diabetes in China and the prevalence of prediabetes was 35.2% in Chinese adults, diagnosed by the ADA criteria, which indicates that diabetes is really an important health problem in China.[8] 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.[9] 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.[10] 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 HbA1c levels, suggesting a need for additional therapeutic options.

Marketed injectable GLP-1R agonists have demonstrated robust glycemic efficacy, weight loss, and cardiovascular safety, with at least one marketed agent demonstrating cardiovascular benefit.[11] Based on the clinical history of injectable GLP-1R agonists, an oral GLP-1R agonist is expected to improve glucose control and reduce HbA1c levels in patients with T2DM, while decreasing food intake and body weight and avoiding the subcutaneous injection required by currently available peptidic GLP-1R agonists.

2.2.1. Nonclinical Overview

2.2.1.1. Nonclinical Pharmacology

In vitro primary pharmacodynamic studies demonstrated that in cells expressing recombinant human and monkey GLP-1R, PF-06882961 concentration-dependently promotes cAMP production. In contrast, no cAMP production was observed in cells expressing recombinant rat, mouse, and rabbit GLP-1R at tested concentrations (<10-20 μM). In addition, PF-06928468 (metabolite of PF-06882961) was found to be inactive against human GLP-1R. PF-06882961 was shown to bind to the human GLP-1R using a competition binding assay. In vivo, PF-06882961 dose-dependently potentiated glucose-stimulated insulin secretion during an IVGTT in cynomolgus monkeys. 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.

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

2.2.1.2. Nonclinical Pharmacokinetics and Metabolism

The oral PK of PF-06882961 in rats and monkeys indicated rapid absorption with bioavailability ranging from 5% to 12%. In repeated oral dose toxicity studies in rats and monkeys, systemic exposure of PF-06882961 increased with increasing dose, with no accumulation.

Metabolism studies showed low turnover of PF-06882961 with some oxidative and glucuronide metabolites. All metabolites detected in human hepatocytes were also observed in hepatocytes from nonclinical species. PF-06882961 is expected to be cleared via hepatic uptake by OATP, followed by metabolic clearance principally mediated by CYP (3A4/5, followed by CYP2C8, and CYP2C19). Non-CYP enzymes also contributed to the metabolism of PF-06882961.

In vitro studies indicate that at doses planned for this study (≤ 120 mg BID), there is a risk of weak pharmacokinetic interaction via time dependent inhibition of CYP3A4 by PF-06882961, and therefore sensitive CYP3A4 substrates with a narrow therapeutic index (TI) will be excluded. Based on in vitro data, PF-06882961 has the potential to inhibit intestinal BCRP, and therefore, rosuvastatin and sulfasalazine, BCRP substrates, are excluded from use in this study.

In vitro data also suggest a risk of PF-06882961 interaction with drugs for which CYP2C8 and UGT1A1 mediated metabolism constitutes the primary mechanism of clearance. Studies

indicate that PF-06882961 has a low potential to cause DDIs as a result of induction of CYP3A4, or inhibition of other CYP enzymes (1A2, 2B6, 2C9, 2C19 or 2D6), other UGT enzymes (1A4, 1A6, 1A9, 2B7, 2B15), and transporters (MDR1, OATP1B1, 1B3, OCT2, MATE1, MATE-2K, OAT1 and OAT3]. See Appendix 7 for a complete list of prohibited medications.

Refer to the IB for more details on the nonclinical PK and metabolism of PF-06882961.

2.2.1.3. Nonclinical Safety

General toxicology studies have been completed in cynomolgus monkeys up to 6 months in duration (with a 3-week lead-in and 1-month recovery) and in rats up to 6 months in duration (with a 1-month recovery). The exposure limits for plasma concentrations of PF-06882961 for clinical studies are based on the exposure at the NOAEL dose of 250 mg/kg/day in the 6-month with 1-month recovery toxicology study in rats, due to the fact that findings in monkeys such as decreased food intake and body weight loss are reversible and monitorable in a clinical setting. In the 6-month toxicity study in rats with 1-month recovery, the NOAEL was 250 mg/kg/day based on species-specific toxicity at a higher dose. The exposure margins at 250 mg/kg/day were 34-fold (C_{max}, free) and 15-fold (AUC_{24}, free), to the observed human exposures at the clinical dose of PF-06882961, 120 mg BID.

A NOAEL was was not established in the cynomolgus monkey 6-month toxicity study with a 3-week lead-in and 1-month recovery, due to early euthanasia of 3 animals administered ≥ 50 mg/kg/day who had clinical signs associated with adverse microscopic findings in the kidney and heart, which was unique to this study and had not been observed in animals exposed for longer duration in previous studies with similar doses. Based on the available data, none of the microscopic findings observed in these moribund animals appear to be consistent with primary toxicological effects. Rather, they are more consistent with secondary events related to prolonged inanition and the resulting negative energy state. Exposure margins at 50 mg/kg/day were 0.60- and 4.3-fold for C_{max} in males and females, respectively, and were 0.27- and 1.5-fold for AUC_{24} in males and females, repectively.

Other toxicology studies completed in cynomolgus monkeys include a 14-week study with a 4-week lead-in (18 weeks total exposure) and a 13-week investigative toxicology study with 3-week lead-in (16 weeks total exposure), in which the NOAEL were the highest doses administered (100 mg/kg/day and 150 mg/kg/day, respectively). At the NOAEL dose of 100 mg/kg/day in the 14-week study with 4-week lead-in, exposure margins were 1.3-fold and 0.75-fold for C_{max} and AUC_{24}, respectively, based on the lack of adverse findings in animals that survived to the scheduled necropsy. At the NOAEL dose of 150 mg/kg/day in the 13-week study with 3-week lead-in, exposure margins were 8.0- and 5.9-fold for C_{max} in males and females, respectively, and were 5.7- and 5.2-fold for AUC_{24} in males and females, repectively, based on the absence of adverse effects in the study.

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

provide margins of approximately 69-fold (C_{max}, free) and 68-fold (AUC_{24}, free), to the observed human exposures at the clinical dose of PF-06882961, 120 mg BID.

In embryo-fetal studies conducted in rabbits, the NOAEL for maternal and developmental toxicity was 250 mg/kg/day, with margins of approximately 15-fold (C_{max}, total) and 3.6-fold (AUC_{24}, total), to the observed human exposures at the clinical dose of PF-06882961, 120 mg BID.

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

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

2.2.2. Clinical Overview

As of the protocol date, 3 clinical studies, C3421001, C3421002, and C3421003 have been completed dosing with PF-06882961. C3421001, which administered single ascending oral doses of PF-06882961 or placebo to healthy adult participants, C3421002, which administered multiple ascending oral doses of PF-06882961 or placebo to adults with T2DM and safety results from this study are provided in Section 2.2.2.1, and C3421003, which administered single oral doses of different formulations of PF-06882961 to healthy participants. Refer to the IB for more details on these studies and the known drug class effects of marketed injectable GLP-1R agonists.

2.2.2.1. Clinical Safety

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

The results of C3421002, which is the only completed multiple dosing study in patients with T2DM to date, are summarized as below.

In Study C3421002, PF-06882961 doses ranging from 10 mg BID to 120 mg BID were generally safe and well tolerated. A total of 98 participants with T2DM on a background of metformin were randomized to receive PF-06882961 or matching placebo in a 3:1 randomization ratio, and 92 participants completed the study. Six (6) participants discontinued from the study, of which 2 discontinuations were due to treatment-related TEAEs, and 4 withdrew during the treatment or follow-up period for non-treatment related reasons. One (1) participant in the 15 mg BID group discontinued from the study due to a treatment related, moderate TEAE of headache on Day 2. One (1) participant in the 50 mg BID group discontinued from the study due to moderate TEAEs of decreased appetite on Day 1, nausea, vomiting, and a mild TEAE of fatigue on Day 7 (all related to study drug).

A total of 319 TEAEs were reported, of which the majority of the AEs [294 (92%)] were mild in intensity, 23 (7%) were moderate, and 2 (1%) were severe in intensity. The most frequently reported TEAEs were nausea (49.0%), dyspepsia (32.7%), vomiting (26.5%), diarrhea (24.5%), headache (23.5%), and constipation (20.4%). One (1) participant

experienced a TEAE of hypoglycemia. This AE was non-fasting, mild in severity and of limited duration.

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

While there were isolated values for laboratory tests, vital signs and ECG intervals outside of the reference ranges, no clear adverse trends were apparent in these parameters. As has been reported for marketed GLP-1R agonists,[11, 12] increases in heart rate have been observed, with mean increases ranging from 5 to 15 bpm across doses administered to date, and most heart rate values were within the normal range. In summary, PF-06882961 was generally safe and well tolerated in C3421002, with a safety profile in line with marketed GLP-1R agonists.

2.2.2.2. Clinical Pharmacokinetics

The clinical PK of PF-06882961 in healthy adult participants has been evaluated in two completed studies: C3421001 and C3421003. The results of these completed studies are summarized in the PF-06882961 IB.

The PK properties of PF-06882961 have been evaluated in adult participants with T2DM as part of the completed C3421002 study. In this study, the first 6 cohorts received PF-06882961 or placebo dosed BID. Dosing for 4 of the 6 cohorts was titrated for various amounts of time over the 28 days, with target maximum doses ranging between 10 and 120 mg BID across the 6 cohorts. Approximately dose proportional increases in C_{max} and AUC_{24} were observed between the doses of 10 mg BID and 120 mg BID, with geometric mean C_{max} ranging from 38.38 to 685.2 ng/mL and AUC_{24} ranging from 455.9 to 8368 ng•h/mL. Percent coefficients of variance (%CV) ranged from 32 to 94 and 41 to 87 for C_{max} and AUC_{24} respectively on Day 28. Consistent with data from the completed studies, PF-06882961 was observed to have a $t_{½}$ of approximately 4.681 to 8.090 hours. Median T_{max} ranged from 3 to 6 hours after the AM dose over the dose ranges administered.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-06882961		
Thyroid C-cell tumors	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, dulaglutide, and exenatide) due to dose-dependent and treatment duration-dependent thyroid C-cell tumors in nonclinical studies in rats and mice at clinically relevant exposures. Thyroid C-cell tumors have not been observed with PF-06882961 in clinical or nonclinical studies.	Potential participants with a personal or family history of medullary thyroid carcinoma or MEN2 are excluded from the clinical development program. Thyroid function tests are included in the clinical trial protocols to monitor participants' thyroid function.
Pancreatitis	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide and dulaglutide). Pancreatitis has not been observed in the PF-06882961 clinical trial program.	Per exclusion criteria, potential participants with acute pancreatitis or a history of pancreatitis are not elgigible for study entry. Serum amylase and lipase are monitored during the clinical studies.
Hypoglycemia	Clinical trials with injectable GLP-1R agonists have not demonstrated an increased risk for hypoglycemia. However, when administered in combination with anti-diabetic agents that are known to have an increased risk of hypoglycemia (such as insulin or sulfonylureas), an increased risk for hypoglycemia was observed. Only one adverse event of mild hypoglycemia has been reported in the clinical development program to date.	Blood glucose is monitored frequently during clinical studies involving patients with T2DM, and hypoglycemia is a well recognized risk in T2DM patients. The IB and ICD inform of the potential increased risk of hypoglycemia when PF-06882961 is administered in combination with anti-diabetic agents that are known to have an increased risk of hypoglycemia (such as insulin or sulfonylureas), which are prohibited in this study.
Impairment in renal function	In rats, minimal renal tubular vacuolation was observed, but this finding was considered to be non-adverse.	Per exclusion criteria, potential participants with significant renal impairment (<60 mL/min/1.73m^2) are not eligible for study entry. Renal function is

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In the clinical trial program only one mild AE (Blood creatinine increased) has been observed.	monitored during the study by the lab assessments of serum BUN, creatinine and eGFR.
Gastrointestinal adverse reactions	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide and dulaglutide). In addition, gastrointestinal AEs, the majority of which were mild in severity, have been observed in the clinical program with PF-06882961. In nonclinical studies with PF-06882961, gastrointestinal adverse effects have been seen in rats and monkeys.	Participants are monitored during the clinical study visits, via body weight, vitals signs and laboratory assessments, to prevent potential sequelae of any severe gastrointestinal reactions, eg, dehydration. Dose titration will be adopted to enhance tolerability to PF-06882961.
Diabetic retinopathy complications	The potential risk is based on the product labeling for the injectable GLP-1R agonist semaglutide for T2DM. This risk has not been listed in the prescribing information for other marketed GLP-1R agonists. There are no nonclinical or clinical data involving PF-06882961 to suggest an increased risk of diabetic retinopathy complications.	Potential participants with a known medical history of active proliferative retinopathy and/or macular edema are excluded from the clinical studies.
Use of a placebo arm.	Participants randomized to placebo may not experience glycemic lowering effect.	A majority of the randomized study population will receive PF-06882961, and all participants will receive lifestyle counseling, which is standard of care for management of T2DM. Participants will be actively monitored and those who experience hyperglycemia, per protocol defined criteria, may be discontinued and receive rescue medication.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
During the COVID-19 pandemic, the following is recommended: Risk COVID-19 contamination during study.	During the pandemic participant could be infected with the the SARS-COV-2 virus through study participation. This could lead to increased health risk for this participant and others in the study. Confounding AE with compound.	COVID-19 specific assessments according to SoA.

2.3.2. Benefit Assessment

Based on the clinical experience of injectable GLP-1R agonists, an oral GLP-1R agonist is expected to improve glucose control, reduce HbA1c levels, diminish food intake, and decrease body weight in patients with T2DM, while avoiding the requirement for subcutaneous injections that accompanies currently available peptidic GLP-1R agonists. As the treatment period of this study is only 8 weeks, clinical benefit to participants with T2DM is unlikely or limited given the short duration of this study and the early stage of development of PF-06882961. This study is designed to generate safety, tolerability, PK CCI [redacted] data in Chinese T2DM participants for further clinical development.

2.3.3. Overall Benefit/Risk Conclusion

In line with the clinical profile of marketed GLP-1R agonists[13, 14, 15], the most frequently reported AEs with PF-06882961 administration have been nausea, diarrhea, dyspepsia, headache, and vomiting. In addition, as has been reported for marketed GLP-1R agonists, increases in heart rate have been observed with PF-06882961 administration, with most heart rate values within the normal range.

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

3. OBJECTIVES , ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To characterize the plasma PK of PF-06882961 following a single oral dose on Day 1 and following multiple, oral doses administered to adult Chinese participants with T2DM.	Not Applicable	• Single dose (10 mg): AUC_{24}, C_{max}. • Multiple dose (40 mg, 80 mg, 120 mg): AUC_{24}, $C_{max,ss}$.
Secondary:	**Secondary:**	**Secondary:**
• To evaluate the safety and tolerability of PF-06882961 following a single oral dose on Day 1 and following multiple, oral doses administered to	Not Applicable	• Vital signs, Electrocardiograms, Adverse events (e.g. hypoglycemia and hyperglycemia), Clinical safety laboratory assessments.

Objectives	Estimands	Endpoints
adult Chinese participants with T2DM.		
CCI		

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, double-blind, sponsor-open, placebo-controlled, oral dosing study of PF-06882961 in adult Chinese participants with T2DM inadequately controlled on diet, exercise and metformin background therapy.

Participants will receive oral doses of PF-06882961 or placebo in this study. Approximately 20 participants will be randomized to PF-06882961 or placebo at a 3:1 ratio (15 participants to PF-06882961 and 5 participants to placebo) such that at least 8 participants in PF-06882961 group will complete 120 mg and be evaluable for PK analysis. The study will be conducted at a single clinical site in China.

The target dose level is PF-06882961 120 mg BID (or matching placebo). Following the screening period to confirm eligibility (up to 4 weeks), the treatment period will be approximately 8 weeks, followed by an approximate 4-week follow-up. The total duration of participation in this study is approximately 12 weeks, not including the screening period. Dosing will occur with food (QD at Day 1 and BID at Days 2-56), and up to 6 weeks of the 8-week dosing duration will be used for dose titration to maximize tolerability of PF-06882961, as depicted in Figure 2. The dose of PF-06882961 will be increased following a prespecified titration scheme during visits V2 through V8 to reach the target dose, which will then be maintained through V10. Downward titration or dosing is not permitted during the study. Participants who do not tolerate the titration scheme and/or assigned dose may be required to discontinue dosing of study intervention. If a participant discontinues the study intervention, every effort should be made to contact the participant for the follow-up visits (V11 and V12).

As shown in Section 1.2, this study includes a total of 12 visits, of which 4 are inpatient study visits at the site (V2, V5, V7, V10) and 5 are outpatient visits (V3, V4, V6, V8, V9) excluding Screening to the site (V1). The others are follow-up visits (V11 and V12). Following the Screening visit (V1) to confirm eligibility (up to 4 weeks), participants will be randomized at V2 to receive PF-06882961 (or matching placebo) for a duration of 8 weeks and complete dosing at V10. The inpatient stays at V2 and V10 consists of 4 days and 3 nights, while the inpatient stays of V5 and V7 consist of 3 days and 2 nights, as listed in the SoA. For the study duration between the inpatient study visits, participants will continue dosing with blinded study intervention either at home, at an outpatient visit, or at the study site as an inpatient. Please refer to Figure 2 for the scheme of dose titration.

Participants who discontinue prior to completion of the study for non-safety related reasons may be replaced, at the discretion of the PI and Sponsor.

4.2. Scientific Rationale for Study Design

The purpose of this study is to evaluate the PK, safety and tolerability of single and multiple oral doses of PF-06882961 in adult Chinese participants with T2DM who are receiving metformin as background antihyperglycemic medication. CCI [redacted]

CCI [redacted] Results from this study will be compared with Global studies (C3421002 and C3421005) to facilitate the analyses of ethnic differences in PK, CCI and tolerability between Chinese and Westerners.

Completed studies indicated that PF-06882961 exposures in T2DM participants was 1.7-fold higher than that in healthy participants, despite higher body weight. In Study C3421002, the steady-state PK of PF-06882961 was characterized in a T2DM population. A similar Chinese population with T2DM was selected in the current study to facilitate the PK comparison of PF-06882961 between Chinese and Western participants. CCI [redacted]

Based on the results from Study C3421002, the starting dose of PF-06882961 in the current study will be set at 10 mg BID (or matching placebo). The dose will then be up-titrated approximately weekly to reach the target level of 120 mg BID at Week 7. Such dose titration was adopted to enhance the tolerability to higher doses of PF-06882961. This titration scheme is identical to that in Global Study C3421005 which permits the comparison of tolerability between Chinese and Westerners. It is considered that gastrointestinal adverse events common to GLP-1R agonists are mostly expected soon after dose increases. Therefore, the 2-week maintenance period of 120 mg BID (Visits 8-10) is sufficient to characterize the safety and tolerability of PF-06882961 in the current China Phase 1 study. Such titration and maintenance period is identical to part of that in Study C3421005 which allows a comparison CCI after 8-week treatment, CCI [redacted] The data will also be pooled with a number of other studies and assessed via population PK and PKCCI analyses. CCI safety data obtained in Chinese participants will be compared with data from Study C3421005 in which similar titration and maitanance schedules were adopted.

A baseline day (Day -1) with time-matched procedures will permit an improved assessment of safety, tolerability, CCI [redacted] The participants and site staff will be blinded to administration of active versus placebo to permit an unbiased assessment of tolerability and safety.

Clinical safety laboratory tests, 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. As part of the clinical safety laboratory tests, calcitonin, amylase, and lipase will be assessed, as these laboratory parameters have been shown to increase with marketed GLP-1R agonists. In addition, TSH, FT4, lipid profile, coagulation profile, and TBA will be assessed, based on non-adverse findings in the nonclinical studies with PF-06882961.

In an effort to reduce variability and better quantify potential changes, all measurements of ECG intervals, heart rate and BP will be collected in triplicate (except as noted in the SoA) and mean values of them will be used for analysis at each time point. In addition to triplicate ECG and BP measurements taken prior to dosing of study intervention, and any morning

dose of permitted concomitant medications, triplicate ECG intervals and BP measurements will also be collected at approximate time for C_{max} CCI on PK sampling days as specified in the SoA to further enhance quantification of any possible drug effect.

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), which are prohibited in this study. Blood glucose concentrations will be monitored throughout the study via glucometer, and monitoring of symptomatic hypoglycemic AEs will be performed. In addition, all participants will be instructed on Day -2 regarding the symptoms associated with, and management of, hypoglycemia, which will permit the monitoring of symptomatic HAEs.

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

The potential risk of exposure to PF-06882961 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[16]

4.3. Justification for Dose

In this study, PF-06882961 will be administered BID in titration: starting with 10 mg and titrated approximately weekly up to 120 mg within 6 weeks, followed by 2-week maintenance at 120 mg. It is considered that steady state is achieved during each weekly titration step. The PF-06882961 doses selected for this study are based on observed safety, tolerability, PK, CCI data from the completed 4-week study comparing PF-06882961 to placebo in T2DM participants (Study C3421002); as well as the exposure margins relative to observed toxicology findings. Exposure margins for the proposed dose in this study (120 mg BID) are given in Section 2.2.1.3.

Doses ranging from 10 mg BID to 120 mg BID were generally safe and well tolerated in Phase 1 Study C3421002. The titration scheme used in this study is slower than that used in C3421002. CCI [redacted]. Given the current dose titration and PK sampling schedule, AUC_{24} and C_{max} parameters from the 40 mg and 80 mg doses will be determined.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the follow up visit (V12).

The end of the study is defined as the date of the last visit (V12) of the last participant in the study.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Chinese male or female participants between the ages of 20 and 60 years, inclusive, at Visit 1 (Screen 1).

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

Type of Participant and Disease Characteristics:

2. 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.

3. HbA1c ≥ 7.0% and ≤ 10.5% at Screening (Visit 1) as assessed by the study specific laboratory and confirmed by a single repeat test, if deemed necessary.

4. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures, including the ability to perform self-tests of blood sugar regularly (see Section 8.2.5.1) for the duration of the study and maintenance of study specific glucose diary for the duration of participation in the study.

Body Mass Index (BMI) and Weight:

5. Total body weight > 50 kg (110 lb) with BMI of 22.5 to 45.4 kg/m^2. Body weight must have been stable (< 5% change) for 90 days prior to Screening (Visit 1) as per participant report.

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

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 participant with hypercholesterolemia on appropriate treatment is eligible).

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

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

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

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

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

7. Acute pancreatitis or history of chronic pancreatitis.

8. Acute gallbladder disease.

9. History of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody (HCVAb) or syphilis. Hepatitis B vaccination is allowed.

10. Known intolerance or hypersensitivity to GLP-1R agonists.

11. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

12. Use of the concomitant therapies listed in Section 6.5 and Appendix 7.

Prior/Concurrent Clinical Study Experience:

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

14. Known prior participation in a trial involving PF-06882961.

Diagnostic Assessments:

15. Screening supine BP ≥ 160 mmHg (systolic) or ≥ 100 mmHg (diastolic), following at least 5 minutes of supine rest. BP should be measured in triplicate and the average of the 3 BP values should be used to determine the participant's eligibility.

16. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF interval > 450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility.

17. A positive urine drug test. ***Note:*** Participants who have been medically prescribed opiates/opioids or benzodiazepines and report the use of these drugs to the investigator at Screening (Visit 1) may be allowed to participate with notification to the sponsor.

18. Participants 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:

    - AST or ALT level ≥ 1.5 ×ULN.
    - Total bilirubin level ≥ 1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.
    - Fasting C-peptide < 0.8 ng/mL.
    - TSH > ULN.
    - Serum calcitonin > ULN.
    - Amylase or lipase > ULN.
    - Fasting blood glucose > 270 mg/dL (15.0 mmol/L).
    - eGFR<60 mL/min/1.73m^2 as calculated by the CKD-EPI equation.[17]

19. FSBG on Day -2 of > 270 mg/dL (15.0 mmol/L).

20. A positive COVID-19 test.

Other Exclusions:

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

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

23. History of sensitivity to heparin or heparin-induced thrombocytopenia ***only if*** heparin is used to flush IV catheters.

24. Participation in formal weight loss program is prohibited during participation in this study.

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

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 8 hours prior to CCI the collection of the first blood sample (eg, glucometer measurement, safety laboratory, PK, CCI assessment) at Screening, each inpatient study day, each outpatient visit, and the follow-up visit.

- Water may be consumed as desired (ad libitum).

- Drinks (except grapefruit or grapefruit related citrus fruit juices – see below) may be consumed with meals and the evening snack.

    - Participants 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.

- Standardized meals will be provided at approximately the same time of day in each inpatient day and outpatient visit as shown in SoA.

- Details on the meals provided to participants at Visit 2 through Visit 10, 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 site. This information will not be collected in the case report form, however may be submitted to the Sponsor upon request.

- Participants will not be required to consume all provided food during standard meals.

- When a meal or snack is scheduled at the same time as an ECG, the meal will be provided after the ECGs are completed.

- On scheduled visits to the site, ***in the morning***, from Visit 2 through Visit 10, participants should be instructed to arrive **without** having morning meal/breakfast, metformin and self-administration of IP. ***Note:*** Participants may take their morning dose of antihypertensive and/or lipid modifying medication per their usual routine, if applicable.

- At Visit 2 through Visit 10, inclusive, the morning meal will be consumed with the study intervention at the site.

- Breakfast will be provided approximately 0800 ± 2 hours in each inpatient day and outpatient visit as shown in SoA.

- Lunch will be provided approximately 4 hours after dosing in each inpatient day, and outpatient visit if needed as shown in SoA.

- Dinner will be provided approximately 10 hours after dosing in each inpatient day as shown in SoA.

- An evening snack may be permitted before 2200 hours.

- Participants will be counseled on appropriate dietary and lifestyle guidelines for T2DM at Visit 2 and asked to maintain these guidelines throughout participation in the study. Counseling on dietary guidelines should be in accordance with local medical standards of care for patients with T2DM.

- IP must be administered BID (QD in the morning on Day 1) with the morning and evening meals, approximately 10 hours apart on non-visit days and unscheduled visit.

5.3.2. Caffeine, Alcohol, and Tobacco

- Caffeine containing products may not be consumed within 2 hours prior to measuring vital signs and ECGs.

- Participants will abstain from alcohol for 24 hours prior to each vistit to the site and continue abstaining from alcohol until completion for all procedures of each visit. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants may use tobacco- or nicotine-containing products, as permitted by the site practices ***except*** as noted below.

    - Use of these products will not be permitted during frequent sampling procedures, and will not be permitted within 2 hours prior to any vital sign and ECG assessments. Use of these products will also not be permitted 2 hours before and 2 hours following any dose of PF-06882961/placebo.

5.3.3. Activity

- Participants 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.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee

will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. All screening procedures must be repeated, and the participant assigned a new 8-digit SSID number.

6. STUDY INTERVENTION

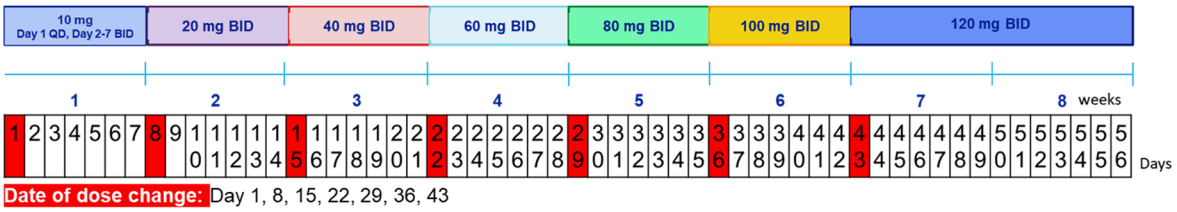
Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to PF-06882961 and matching placebo tablets.

6.1. Study Intervention(s) Administered

For this study, PF-06882961 and matching placebo tablets will be administered orally BID (QD in the morning on Day 1) with morning and evening meals. Please refer to Figure 2 for the scheme of dose titration.

Figure 2. Dose Titration Scheme



PF-06882961 and placebo tablets will be supplied to the site as packaged blisters cards and labeled according to local regulatory requirements.

Intervention Name	PF-06882961	Placebo for PF-06882961
ARM Name	Active	Placebo
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strengths	10 mg, 40 mg and 100 mg	Not applicable
Dosage Levels	10, 20, 40, 60, 80, 100, 120 mg BID (QD on Day 1)	0 mg BID (QD on Day 1)
Route of Administration	Oral	Oral
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the IP Manual.	Provided centrally by the sponsor. Refer to the IP Manual.
Packaging and Labeling	Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement. Blinded labels will be utilized for titration and stable dosing blister packs.	Study intervention will be provided in blister packs. Each blister pack will be labeled as required per country requirement. Blinded labels will be utilized for titration and stable dosing blister packs.

6.1.1. Administration

Participants will take 3 tablets of study intervention (PF-06882961 or matching placebo) with the morning meal and 3 tablets of study intervention with the evening meal, approximately 10 hours apart and at approximately the same time each day for a total of 6 tablets of study intervention (PF-06882961 or matching placebo) daily, except on Day 1. Participants will swallow the study intervention whole, and will not crush, chew, break, or dissolve the study intervention prior to swallowing. Downward titration or dosing is not permitted during the study; participants who do not tolerate the titration scheme and/or assigned dose may be required to discontinue dosing of study intervention.

The titration schemes to be used in this study and additional details regarding titration are provided in Section 1.2, Table 3 and the IP Manual.

6.1.1.1. Inpatient and outpatient visit days

Morning dosing at approximately 0800 ± 2 hours and evening dosing at approximately 1800 ± 2 hours and the interval between them should be about 10 hours. Dosing will occur with food at the site on admission and during inpatient days in V2, V5, V7, and V10, except discharge days (Days 2, 22, 36). For discharge days and outpatient visit days, morning dosing at approximately 0800 ± 2 hours will occur with food at the site. Participants will be instructed to arrive at the site in the fasted state for each of scheduled visits. For V3-V10, participants will be instructed to bring their study intervention supply and dosing diary with them, and to withhold self-administration of study intervention on scheduled visit days until they are directed to dose during their visit. When participants dose at the site, they will self-administer the study intervention under supervision by site staff. The date and time of each dose administered at the site will be recorded in the site source documents, in the diary and in the CRF. Additionally, the date and time of the previous 2 doses of double-blinded study

intervention prior to each of the pre-dose PK blood collections (ie, the 2 most recent doses prior to the visit as noted in the diary) will be entered in the CRF.

Administration of blinded study intervention for all dosing regimens will occur under the conditions described in Section 5.3.1.

6.1.1.2. Non-visit days

Dosing and administration instructions along with a dosing diary, will be provided to participants to support at home dosing of study intervention. When participants self-administer the study intervention at home, they will record each dose in the diary.

Participants will be instructed to self-administer their study intervention according to administration instructions provided to the participant.

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

6.2. Preparation/Handling/Storage/Accountability

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

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

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

5. Study interventions should be stored in their original containers.

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

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using the IRT system via unique container numbers in the blister cards provided, in quantities appropriate according to the SoA. A second staff member will verify the dispensing. The participant/caregiver should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files. Study

intervention will be dispensed at the study visits summarized in the SoA. Returned study intervention must not be redispensed to the participants.

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

A randomization code using the method of random permuted blocks will be utilized to randomize eligible participants in 3:1 ratio (PF-06882961 : placebo) prior to the first dose of study intervention.

Participants will receive the following number of tablets and corresponding dose level described in Table 3.

Table 3. Dose Levels in Study C3421028

Dose Level Description (dosed BID)	Number of PF-06882961 tablets			Number of PF-06882961-matching placebo tablets
	10 mg	40 mg	100 mg	10/40/100 mg
Placebo	-	-	-	3
PF-06882961 – 10 mg	1	-	-	2
PF-06882961 – 20 mg	2	-	-	1
PF-06882961 – 40 mg	-	1	-	2
PF-06882961 – 60 mg	2	1	-	-
PF-06882961 – 80 mg	-	2	-	1
PF-06882961 – 100 mg	-	-	1	2
PF-06882961 – 120 mg	2	-	1	-

6.3.2. Breaking the Blind

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

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

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. The investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. Other specified Pfizer personnel will be

unblinded to study treatment in order to permit review of the safety, PK CCI data. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed and study database has been locked. Specimens from participants randomized to placebo will not be routinely analyzed. 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, blinded investigator site personnel, or blinded study monitor until the study database has been locked or the investigator requests unblinding for safety reasons.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the site will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF. At each visit from V3 to V10, site should assess the blister cards for compliance. Compliance (as assessed by tablet count) will be defined as self-administration, by the participants of ≥ 80% of the study supplied study intervention from Day 1 through Week 8, inclusive. Investigators must closely follow non-compliant, randomized, participants in order to enhance their adherence to treatment.

Any participant who fails to meet the criterion of ≥ 80% compliance will be re-educated by the site staff on the importance of compliance with study intervention.

A record of the number of study intervention tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

The background metformin therapy should also be recorded in the diary. Investigators must also closely follow non-compliant participants in order to enhance their adherence to metformin background treatment.

6.5. Concomitant Therapy

Participants in this study will be allowed to be on certain concomitant medications that have been prescribed. Attempts should be made not to alter the doses and regimens of the background medications after randomization and for the duration of participation in this study, except in circumstances where a change in dose is deemed medically necessary. Any

changes must be captured in the CRF. Additionally, many over-the-counter medications are also permitted during this study.

See Appendix 7 for details regarding prohibited concomitant medications. Site are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

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

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

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

6.5.1. Medications for Glycemic Control

All participants are required to be taking metformin monotherapy as their only anti-hyperglycemic treatment prior to inclusion in this study, as listed in Section 5.1. At Screening, this study requires that participants have been taking a stable metformin dose of ≥ 500 mg/day for at least 2 months prior to the Screening visit. The dose of metformin will remain the same total daily dose that was prescribed prior to study entry until completion of study participation (ie, Follow-up visit), except in circumstances where a change in dose is deemed medically necessary. Any changes in doses of metformin must be captured in the CRF. For study visit days, participants should be instructed to refrain from morning dosing at home and to bring the metformin to the site for dosing at the same time as their blinded IP. For participants taking metformin more than once a day, the timing should be approximately the same on each day.

The use of other medications for glycemic control is not permitted in this study (see Appendix 7).

6.5.2. Antihypertensive Medications

The use of background antihypertensive agent(s) is permitted unless otherwise noted in Appendix 7. Doses of antihypertensive agent(s) must be stable for at least 4 weeks prior to Screening and throughout the study, except in circumstances where a change in dose is deemed medically necessary. Any changes in doses of these medications must be captured in the CRF.

6.5.3. Lipid-Modifying Medications

The use of background lipid modifying agents is permitted unless otherwise noted in Appendix 7. Doses of such lipid modifying agents must be stable for at least 4 weeks prior to Screening and throughout the study, except in circumstances where a change in dose is

deemed medically necessary. Any changes in doses of these medications must be captured in the CRF.

6.5.4. Management of Nausea and Vomiting

Nausea and vomiting have been reported with administration of GLP-1R agonists. Participants 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 may be administered at the investigator's discretion with notification to the sponsor and entry in the CRF.

6.5.5. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with study intervention; standard medical supportive care must be provided to manage the AEs. Standard medical supportive care must be provided to manage the AEs, including administration of carbohydrates to treat HAE (see Section 8.2.5.2.1). Please also see Sections 8.2.5.2 and 8.2.5.3 for management of hypoglycemia and hyperglycemia, respectively.

6.6. Dose Modification

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

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- Criteria for a potential DILI (Hy's law) case are met (see Appendix 5);
- Intent to become pregnant or pregnancy confirmed by serum β-hCG testing;
- Safety or tolerability concern arises, in particular if not responsive to symptomatic management, dosing with double-blind study intervention may be stopped in an individual participant at the discretion of the investigator.

If the criteria for permanent discontinuation are met, the site should notify the sponsor Medical Monitor or sponsor Clinician.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for protocol-specified follow-up procedures as depicted in the SoA. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

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

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) 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.

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

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

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

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

The total blood sampling volume for individual participants in this study is approximately 350 mL and will follow the requirements of laboratory. 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.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments

Efficacy assessments are not evaluated in this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A physical examination will include, at a minimum, assessments of the head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. Height and weight will also be measured and recorded.

Physical examinations must be conducted by a physician.

Height will be measured at Screening only.

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

CCI [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted].

8.2.3. Vital Signs

Supine BP will be measured with the participant'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. Participants should be

instructed not to speak during measurements. When a meal or snack is scheduled at the same time as measuring BP and PR, the measuring BP and PR must be performed prior to the meal/snack. When triplicate BP and PR are required, they will be obtained approximately 2 to 4 minutes apart; the average of the triplicate BP and PR measurements collected at each nominal time point on Day -1 will serve as each participant'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.

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

8.2.4. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant 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 5 minutes apart; the average of the triplicate ECG measurements collected at each nominal time point on Day -1 will serve as each participant's time-controlled baseline QTcF value.

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

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

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time 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.

ECG values of potential clinical concern are listed in Appendix 6.

8.2.5. Management of Glycemic Control

HAEs and FPG will be routinely monitored during participation in the study.

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

8.2.5.1. Home Glucose Monitoring

- To aide in management of their T2DM, all participants will be provided home glucose monitoring supplies including a glucometer, instructions on the use of the glucometer and accompanying supplies.

- Home glucose monitoring diary will be provided to participants for completion at home and brought to each visit to the site along with the glucometers. Investigators must review the home glucose monitoring diary completed by the participants and the readings stored in the glucometer device at all time points listed in the SoA.

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

- Less frequent glucose monitoring will NOT be considered a protocol deviation unless the participant fails to monitor his/her glucose for 3 or more consecutive days.

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

8.2.5.2. Management of Hypoglycemia

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), which are prohibited in this study. Blood glucose concentrations will be monitored throughout the study via glucometer, and monitoring of symptomatic hypoglycemic AEs will be performed. In addition, all participants will be instructed on Day -2 regarding the symptoms associated with, and management of, hypoglycemia, which will permit the monitoring of symptomatic HAEs.

Any episode of hypoglycemia must be captured on the Adverse Event Form CRF with specific details captured on the Hypoglycemic Event Details CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.2.5.2.1 below.

Participants noted to have a fasting glucose value (during home glucose monitoring) meeting the definition of hypoglycemia must be instructed to repeat the measurement the next day

(following at least an 8 [preferably 10] hour fast, except water). If the second measurement also meets the below definition, participants must be asked to return to the site within 1 to 3 days (following at least an 8 [preferably 10] hour fast, except water) and have blood collected and sent to the laboratory for analysis of FPG.

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

Based on review of the participant completed home glucose monitoring dairy at each time point specified in the SoA, as well as results reported by the laboratory, the investigator must assess the glucose values as well as any symptoms documented.

HAE is defined as **one** of the following:[18, 19]

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

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

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

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

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

2. The participant exhibited at least one of the following neurological symptoms:

   - Memory loss;
   - Confusion;
   - Uncontrolled behavior;
   - Irrational behavior;

- Unusual difficulty in awakening;
- Suspected seizure;
- Seizure;
- Loss of consciousness.

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

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

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

8.2.5.3. Management of Hyperglycemia

Hyperglycemia is defined as the following:

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

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

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

If the results from the laboratory confirm the readings using glucometer, the participant should be discontinued, and the investigator will recommend further appropriate glycemic treatment according to the local healthcare standards and national guidelines.

8.2.6. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

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

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

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.7. COVID-19 Specific Assessments

Participants will be tested for SARS-COVID-19 infection on Screening visit and a subsequent COVID-19 test will be performed if the participant has exposure to COVID-19 positive subject, or residence or travel in area of high incidence, or develop COVID-19 related signs and symptoms. The test may be adjusted or additional test may be required by local regulations or by the Principal Investigator.

Exposure to positive subject, residence or travel in area of high incidence and COVID-19 related signs and symptoms will be checked, at least 48 hours before and at each visit. COVID-19 temperature checking will be done at least daily during residence.

8.2.8. Pregnancy Testing

Pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at Screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant’s receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations.

8.3. Adverse Events and Serious Adverse Events

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

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

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

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in

Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposed a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by all possible routes of exposure, eg, ingestion, inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by all possible routes of exposure, eg, ingestion, inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, 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. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

Abnormal pregnancy outcomes are considered SAEs. 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), 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 including 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 study intervention.

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental

exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so 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.

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, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

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

8.3.6. Cardiovascular and Death Events

This part is not applicable in this study.

8.3.7. Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs

This part is not applicable in this study.

8.3.8. Adverse Events of Special Interest

This part is not applicable in this study.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

This part is not applicable in this study.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 12 tablets within a 24-hour time period ± 2 hours will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06882961 (whichever is longer).

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Safety **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

8.5. Pharmacokinetics

Blood samples of approximately 3 mL, to provide a minimum of 1 mL plasma, will be collected for measurement of plasma concentrations of PF-06882961 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to 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 the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of PF-06882961. Samples collected for analyses of PF-06882961 plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, CCI

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-06882961 will be analyzed using a validated analytical method in compliance with applicable 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.

Drug concentration information that would unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

There is no statistical hypothesis tests planned for this study and estimand is not applicable.

9.2. Sample Size Determination

The sample size of this study is not based on statistical considerations. A sufficient number of participants will be screened to achieve approximately 20 participants randomly assigned to study intervention and at least 8 evaluable participants completing multiple titration dosing up to 120 mg in order to evaluate the primary endpoints of AUC_{24} and $C_{max,ss}$ at Day 56.

The participants will be randomized at a 3:1 ratio with 15 participants being randomized to PF-06882961 and 5 participants being randomized to placebo for the purpose of descriptively evaluating the safety CCI endpoints. CCI

9.3. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Defined Analysis Set	Description
PK Concentration Analysis Set	It is defined as all participants randomized and treated with PF-06882961 who have at least 1 plasma concentration value collected. The PK concentration analysis set will be used for plasma concentration summaries and plots.
PK Parameter Analysis Set	It is defined as all participants randomized and treated with PF-06882961 who have at least 1 of the PK parameters of interest. The PK parameter analysis set will be used for analyses on the PK parameters.
CCI [redacted]	[redacted]
Safety Analysis Set (SAS)	It is defined as all participants who are randomized and receive at least one dose of study medications. The safety population will be used for the safety analyses.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General Considerations

In general, PF-06882961 plasma PK concentration and parameters data will be summarized descriptively for single dose and multiple doses separately; safety endpoints will be summarized by treatment group and dose levels; CCI [redacted]

9.4.2. Primary Endpoint(s)

AUC_{24}, C_{max}, $C_{max,ss}$ will be summarized descriptively with n, arithmetic mean, standard deviation, coefficient of variatiation (CV%), geometric mean, geometric CV (%), median, minimum, and maximum. Box and whisker plot of individual and geometric mean will be presented.

Concentration data will be listed and summarized descriptively by PK sampling time and day (dose). Summary profiles (mean and median) of the plasma concentration-time data will be plotted by day (dose) against nominal PK sampling time. Mean and median profiles will be presented on both linear-linear and loglinear scales. Spaghetti plots of individual plasma concentration-time data will be plotted by day (dose) and actual PK sampling time.

The PK parameters to be assessed in this study, their definition and method of determination are outlined in the following Table 4. For summary statistics and summary (mean and median) plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

Table 4. Definition of Plasma PK Parameters for PF-06882961

Parameter	Day 1 (D1) or Steady State (SS)	Definition	Method of Determination
C_{max}	D1 & SS	Maximum observed concentration observed from time zero to 24 hours	Observed directly from data
C_{max1} and C_{max2}	D1 & SS	$Cmax_1$: maximum plasma concentration during the dosing interval τ_1 =0 to 10 hours $Cmax_2$: maximum plasma concentration during the dosing interval τ_2=10 to 24 hours	Observed directly from data
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
CCI [redacted]	[redacted]	[redacted]	[redacted]
AUC_{tau1} and AUC_{tau2}	SS	Area under the plasma concentration-time profile from time zero to time tau, where tau1 = 0 to 10 hours and tau2 = 10 to 24 hours	Linear/Log trapezoidal method
AUC_{tau1} (dn) and AUC_{tau2} (dn)	SS	AUC_{tau1} and AUC_{tau2} normalized to a 1 mg dose	AUC_{tau1}/Dose AUC_{tau2}/Dose
AUC_{24}	D1	Area under the plasma concentration-time profile from time zero to time 24 hours	Linear/Log trapezoidal method
AUC_{24}	SS	Area under the plasma concentration-time profile from time zero to time 24 hours	AUC_{tau1} + AUC_{tau2}
AUC_{24} (dn)	D1 & SS	AUC_{24} normalized to a 1 mg dose.	AUC_{24}/Total Daily Dose
CCI [redacted]	[redacted]	[redacted]	[redacted]

Table 4. Definition of Plasma PK Parameters for PF-06882961

Parameter	Day 1 (D1) or Steady State (SS)	Definition	Method of Determination
			CCI
CCI			

9.4.3. Secondary Endpoint(s)

Please refer to Section 9.4.5.

CCI

9.4.5. Other Safety Analyses

Adverse events, ECGs, vital signs and safety laboratory, urinalysis data will be reviewed on an ongoing basis during the study and summarized in a clinical study report to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and PR 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, as applicable, collected during the course of the study will be considered as source data and will not be captured for inclusion into the study database, unless otherwise noted. However, any untoward findings identified on physical exams conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered source data, and will not be captured for inclusion into the study database, unless otherwise noted. Demographic data collected at Screening will be included in the study database.

Safety data will be presented in tabular format according to the sponsor's reporting standards.

9.4.5.1. Electrocardiogram Analyses

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

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

Safety QTc Assessment

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

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

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

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

A copy of the ICD(s) must be provided to the participant.

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

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

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

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will 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 participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the clinical monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan Study and Site Start and Closure.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

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

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests (Table 5) will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 5. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine eGFR CCI Calcium Sodium Potassium Chloride AST ALT Total bilirubin GGT Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a] Urine pregnancy test	CCI Lipid panel: • Total cholesterol • Direct LDL-C • HDL-C • Triglycerides TSH Free T4 Calcitonin Amylase Lipase ***Serum*** total bile acids PT/INR/aPTT Serum pregnancy test (β-hCG) <u>At Screening and/or Day-2 only:</u> • FSH[b] • Urine drug screening[c] • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody • Human immunodeficiency virus • Syphilis • Plasma C-peptide • COVID-19 pathogen by PCR • Antibodies test of COVID-19
	Additional Tests (Needed for Hy's Law)		

Table 5. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT (repeat) PT/INR (repeat) 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 confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).

Investigators must document their review of each laboratory safety report.

CCI [redacted]

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

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

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

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording/Reporting

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

events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

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

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

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

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

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

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition, a second effective method of contraception, as described below, must be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

3. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as SAEs

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  - In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

10.7. Appendix 7: Prohibited Prior/Concomitant Medications

The use of the following classes of agents is not permitted within the timeframe indicated in Table 6 and for the duration of participation in the study. If a participant receives a prohibited medication, the investigator should contact the Sponsor Clinician or Sponsor Medical Monitor to determine if the participant may remain in the study.

Table 6. Prohibited Prior/Concomitant Medications

Drug Classes and/or Drugs	Timeframe of Restriction Prior to Screening Visit
Thiazolidinediones (TZDs) such as pioglitazone.	3 Months
Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, dulaglutide, semaglutide). ***Note:*** Short-term (ie, ≤7 days) insulin administration is permitted if participant is hospitalized.	3 Months
Oral GLP-1 receptor agonists such as oral semaglutide.	3 Months
Other oral anti-diabetic medications, including: · Biguanides except metformin. · Sulfonylureas such as acetohexamide, chlorpropamide, glyclopyramide, glibenclamide, gliclazide, glimepiride. · Meglitinide analogues such as repaglinide, nateglinide, mitiglinide. · Dipeptidyl peptidase 4 inhibitors (DPP 4i) such as sitagliptin, alogliptin, saxagliptin, linagliptin, vildagliptin, teneligliptin, anagliptin, trelagliptin, omrigliptin. · α glucosidase inhibitors such as acarbose, voglibose, miglitol. · Sodium glucose cotransporter 2 (SGLT2) inhibitors such as ipragliflozin, luseogliflozin, tofogliflozin, canagliflozin, empagliflozin, dapagliflozin, ertugliflozin. · Anti-hyperglycemic medications, including bromocriptine and colesevelam.	4 Weeks
Systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide. ***Note*:** As an exception, steroid-containing inhalers, nasal sprays and topical formulations are permitted. ***Note*:** Intercurrent treatment with systemic corticosteroids during participation in the study may be permitted if treatment does/will not exceed 7 days.	4 Weeks
Immunosuppressants such as cyclosporine and tacrolimus.	4 Weeks
Appetite or weight modifying medications, including nonprescription or herbals.	4 Weeks
Pharmacological agents with approved indication for weight loss such as mazindol.	4 Weeks
Anti-psychotic medications such as olanzapine, risperidone.	4 Weeks

Table 6. Prohibited Prior/Concomitant Medications

Drug Classes and/or Drugs	Timeframe of Restriction Prior to Screening Visit
Coumarin type anticoagulants or other anticoagulants (eg, dabigatran).	4 Weeks
Anticonvulsants if prescribed for seizure disorder.	4 Weeks
Antiarrhythmic medications whose primary mechanism of action is sodium or potassium channel blockade (eg, procainamide, quinidine, proprafenone; as well as amiodarone, sotalol). ***Note*:** β-adrenergic receptor blocking agents (eg, atenolol, metoprolol) and calcium channel blockers (eg, diltiazem, amlodipine, nifedipine) are permitted.	4 Weeks
Sympathomimetic agents. ***Note*:** Inhaled β-adrenergic receptor agonists (eg, albuterol) are permitted.	4 Weeks
Rosuvastatin. ***Note*:** Other statins are permitted.	4 Weeks
Sulfasalazine	4 Weeks
Use of CYP3A4/5 substrates with narrow therapeutic index – eg, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus.	4 Weeks
Use of chronic agents which are potent inducers of CYP3A (eg, rifampin).	4 Weeks
Use of chronic agents which are clinically significant OATP inhibitors (eg, cyclosporine, rifampin).	4 Weeks
Use of potent 3A4 inhibitors. ***Note:*** Short term use of potent CYP3A inhibitors (eg, ketoconazole, itraconazole) for management of fungal infections ≥4 weeks prior to Visit 1 (Screening) is acceptable but use must be avoided post randomization.	4 Weeks
Paclitaxel, torsemide.	4 Weeks
Herbal supplements and other natural products (including Traditional Chinese Medicine).	4 Weeks

10.8. Appendix 8: Abbreviations

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

Abbreviation	Term
%CV	coefficient of variation, percent
Abs	absolute
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
CCI [redacted]	[redacted]
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{tau}	area under the concentration-time curve at steady state over the dosing interval τ
AV	atrioventricular
BCRP	breast cancer resistance protein
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
CCI [redacted]	[redacted]
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CCI [redacted]	[redacted]
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration, steady state
CCI [redacted]	[redacted]
CONSORT	Consolidated Standards of Reporting Trials
COVID	coronavirus disease
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury

Abbreviation	Term
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DPP-4i	dipeptidyl peptidase-4 inhibitors
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EFD	embryo-fetal developmental
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
CCI	[redacted]
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
FT4	free thyroxine
FU	follow up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
HAE	hypoglycemic adverse event
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HDL-C	high-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual

Abbreviation	Term
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IVGTT	intravenous glucose tolerance test
IWR	interactive Web-based response
LBBB	left bundle branch block
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR1	multidrug resistance mutation
MEN2	multiple endocrine neoplasia syndrome type 2
CCI	[redacted]
msec	millisecond
MTC	medullary thyroid carcinoma
N/A	not applicable
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptides
OCT	organic cation transporter
PCR	polymerase chain reaction
CCI	[redacted]
pH	potential of hydrogen
PI	Principal Investigator
PK	pharmacokinetic(s)
POC	proof of concept
PR	pulse rate
PT	prothrombin time
CCI	[redacted]
PVC	premature ventricular contraction/complex
QD	once daily
QRS	time from ECG Q wave to the end of the S wave corresponding to ventricle depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SGLT2	Sodium glucose cotransporter 2
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
ss	steady-state
SSID	study-specific subject identification
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
T2DM	type 2 diabetes mellitus
T4	thyroxine
TBA	total bile acids
TBili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TI	therapeutic index
CCI	[redacted]
TSH	thyroid stimulating hormone
TZDs	Thiazolidinediones
UGT	uridine 5'-diphospho-glucuronosyltransferase glucuronosyltransferase
ULN	upper limit of normal
US	United States
V#	Visit, where # is a numerical value
CCI	[redacted]
WBC	white blood cell
WOCBP	woman of childbearing potential

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