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

Study Intervention Number:	PF-06882961
Study Intervention Name:	N/A
US IND Number:	[redacted]
EudraCT Number:	N/A
Protocol Number:	C3421015
Phase:	1

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

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Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	30 June 2020	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

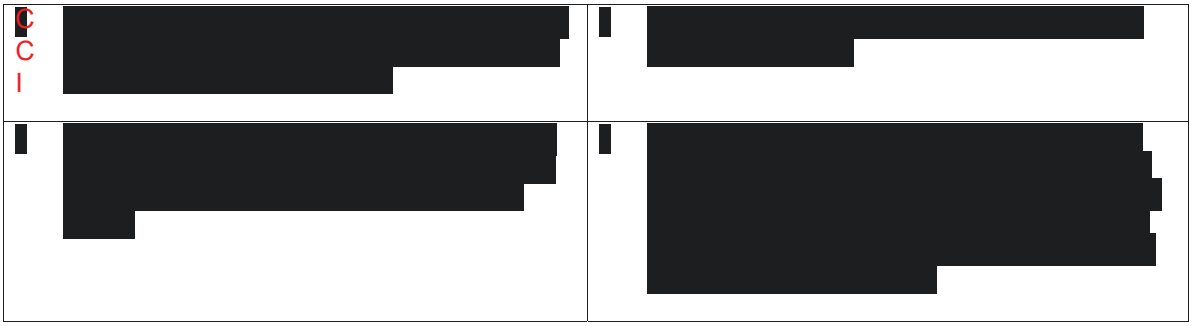
Short Title: A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of PF-06882961 in Japanese Adults with Type 2 Diabetes Mellitus

Rationale

The purpose of the study is to evaluate the safety, tolerability, and PK of multiple oral doses of PF-06882961 in adult Japanese participants with T2DM. CCI [redacted]

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of multiple, oral doses of PF-06882961, administered to adult Japanese participants with T2DM.	• Incidence of treatment emergent AEs (AEs and SAEs), clinical laboratory abnormalities, vital signs and ECG parameters during the entire study.
Secondary:	**Secondary:**
• To characterize plasma pharmacokinetics of PF-06882961 following Day 1 and following multiple, oral doses administered to adult Japanese participants with T2DM.	• PF-06882961 plasma pharmacokinetic parameters AUC_{24}, C_{max}, T_{max}, $t_{½}$ (as defined in Section 9.4.3.1, as appropriate for the dosing paradigm) following Day 1, and multiple dose administration, as data permit.
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]



Overall Design

This is a Phase 1, randomized, double-blind (sponsor-open), placebo-controlled, 4-arm, parallel group study of PF-06882961 in adult Japanese participants with T2DM inadequately controlled on diet and exercise alone.

Participants will receive oral doses of PF-06882961 or placebo in this study. Approximately 9 participants will be enrolled in each arm, for a total of approximately 36 (4 arms) participants randomized. The randomization ratio will be 1:1:1:1 (1 of 3 active dosing regimens of PF-06882961 or placebo), and all 4 arms will be enrolled in parallel. The study will be conducted at a single clinical site in Japan.

Target dose levels, achieved after completion of titration, for the 4 arms of the study are placebo and PF-06882961 doses of 40 mg BID, 80 mg BID, and 120 mg BID. Dose titration will be incorporated to enhance tolerability to PF-06882961.

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.

Number of Participants

A sample size of approximately 36 participants (approximately 9 participants in each of the placebo and 3 PF-06882961 arms) has been selected empirically to permit adequate characterization of safety, tolerability, PK CCI at each dose level in Japanese participants with T2DM.

Intervention Groups and Duration

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. Dosing will occur with food BID, and up to 2 weeks (The target dose level: 40 mg BID), 4 weeks (The target dose level: 80 mg BID) or 6 weeks (The target dose level: 120 mg BID) of the 8-week dosing duration will be used for dose titration to maximize tolerability of PF-06882961.

Participants will take 3 tablets of study intervention (PF-06882961 or matching placebo) in the morning with food and 3 tablets of study intervention in the evening with food,

approximately 10-12 hours apart and at approximately the same time each day. Participants will take a total of 6 tablets of study intervention (PF-06882961 or matching placebo) daily. 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.

Dose Levels in Study C3421015

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	-

Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

Statistical Methods

All treatment arms of PF-06882961 and placebo will be reported separately.

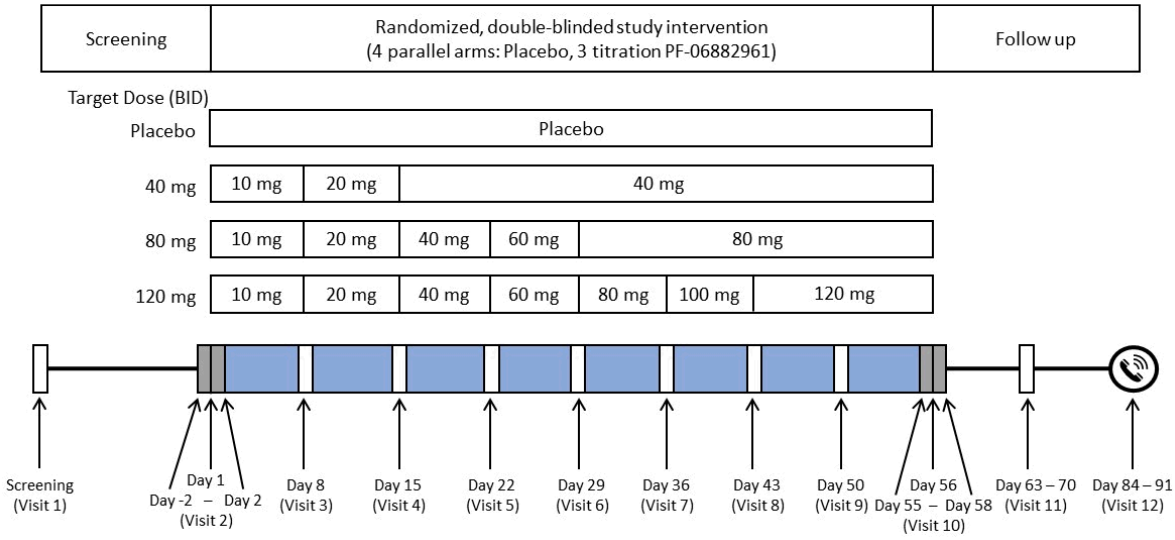
All safety and tolerability analyses will be performed on the safety population.

AEs, ECGs, BP, PR, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study 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.

The plasma PK parameters will be summarized descriptively by treatment, dose and day, as appropriate.

1.2. Schema

Figure 1. Schema of Study C3421015



1.3. Schedule of Activities

The SOA tables (Table 1 and Table 2) provide 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

Protocol Activity (See Appendix 10 for abbreviations)	Screen	Study Day (all activities at 0H [prior to AM meals/dosing] unless otherwise specified)												Follow Up		ET
Visit	V1	V2		V3	V4	V5	V6	V7	V8	V9	V10			V11	V12[a]	
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[b]	-28 to -3	Day -2 to Day 1	2	8	15	22	29	36	43	50	Day 55 to Day 56	57	58	63 - 70	84 - 91	
Informed consent & demography	x	Inpatient stay at study site (See Table 2 For details)									Inpatient stay at study site (See Table 2 For details)					
Review of eligibility criteria	x															
Discharge from inpatient stay			x										x			
Outpatient visit (after ≥8-H fast)	x			x	x	x	x	x	x	x				x		
Adverse event monitoring	x		x	x	x	x	x	x	x	x		x	x	x	x	x
Medical history	x															
Review prior and concomitant treatments	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
Review contraception use (females only)	x			x	x	x	x	x	x	x				x	x	x
Review dosing diary, glucometer & glucose log				x	x	x	x	x	x	x				x[c]		x
Glucose measurement (8 hours fasting, via glucometer, on site)			x	x	x	x	x	x	x	x		x		x		
Physical examination (height at screening only)[d]	x											x		x		x
CCI																
Supine vital signs[f]	x			x	x	x	x	x	x	x		x		x		x
Supine 12-lead ECG[g]	x				x		x		x			x		x		x
Dispensation of study intervention			x	x	x	x	x	x	x	x						
On-site study intervention administration with meal[h]			x	x	x	x	x	x	x	x						
Standardized meals/snacks			x	x	x	x	x	x	x	x		x	x			
Blood sampling for:																
CCI																
Hematology, chemistry (inc. eGFR)	x				x		x		x			x		x		x
CCI																
Lipids, TSH, free T4, calcitonin, amylase, lipase, TBA, PT/INR/aPTT	x						x					x		x		x

Protocol Activity (See Appendix 10 for abbreviations)	Screen	Study Day (all activities at 0H [prior to AM meals/dosing] unless otherwise specified)												Follow Up		ET
Visit	**V1**	**V2**		**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**			**V11**	**V12[a]**	
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[b]	**-28 to -3**	**Day -2 to Day 1**	**2**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**Day 55 to Day 56**	**57**	**58**	**63 - 70**	**84 - 91**	
FSH (females only)	x															
HIV, HepBsAg, HepBcAb, HCVAb, syphilis	x															
Pregnancy test (females only)	x			x	x	x	x	x	x	x				x		x
PF-06882961 PK[i]			x		x		x		x	x		x	x			x
CCI																C
Urine Sampling for:																
Urine drug test	x															
Urinalysis (and microscopy, as appropriate)	x				x		x		x			x		x		x
On-site urine pregnancy test (females only)[j]				x	x	x	x	x	x	x				x		x

a. Contact may occur via telephone and must occur 28 to 35 days from administration of the final dose of study intervention.

b. Allowable time window for V3-V10 is ±1.

c. Review glucometer and glucose log only.

d. Physical examination may be performed at non-specified visits if there are findings during the previous exam or new/open AEs, if appropriate and at investigator discretion.

C [redacted]

f. Includes blood pressure and pulse rate; vital signs at Follow up, and early termination visit (if appropriate) are single; Triplicate vital signs should be conducted at Screening, 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 vital signs collected at 0H only. When a meal or snack is scheduled at the same time as vital signs, vital signs must be obtained prior to the meal/snack (See Appendix 9).

g. 12-lead ECG at Screening, Days 15 and 43, 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 Day 29. 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 (See Appendix 9).

h. During inpatient stays, both AM and PM dosing will occur on the study site, except discharge day (Day 2). On outpatient visit and discharge day, AM dosing will occur at the study site, if applicable.

i. PK samples to be collected prior to AM dose and at 4H after AM dose on Days 15, 29, and 43. Day 2 sample to be collected at 24H after AM dose on Day 1. Day 50 sample to be collected at 24H after AM dose on Day 49. 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.

j. 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: Visit 2 (V2) and Visit 10 (V10)

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

Study Day[a]	Day -2 (V2) Day 55 (V10)	Day -1 and Day 1 (V2) Day 56 (V10)												
Hours Relative to Dosing at 0H[b]	**-**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**
Admission (after ≥8-H fast) and continued inpatient stay at study site	x	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse event monitoring	x	→	→	→	→	→	→	→	→	→	→	→	→	→
Review prior and concomitant treatments	x	→	→	→	→	→	→	→	→	→	→	→	→	→
Review contraception use (females only)	x													
Review of eligibility criteria (Day -2 only)	x													
Counseling on diet/exercise guidelines (Day -2 only)	x													
Dispense glucometer and supplies, dosing diary, glucose log & provide training (Day -2 only)	x													
Review dosing diary, glucometer & glucose log (Day 55 only)	x													
Glucometer measurement (8 hours fasting, via glucometer)	x[c]	x[c]												
Triplicate, supine vital sign assessment[d]		x			x		x		x		x		x	
Triplicate, supine 12-lead ECG		x			x		x		x		x		x	
CCI														
Randomization in trial (Day 1 only)		x												
Study intervention administration with meal (starting on Day 1 and thereafter)	x	x[f]										x		
Mixed Meal Tolerance Test (Days -1 and 56 only)		x												
Standardized meal/snack[g]	x	x[h]							x			x		x
Blood sampling for:														
Hematology, chemistry (inc. eGFR) (Day -1 and 56 only)		x[i]												
CCI Lipids, TSH, free T4, calcitonin, amylase, lipase, TBA, PT/INR/aPTT (Day -1 and 56 only)		x[i]												
CCI														
Pregnancy test (females only)	x													
PF-06882961 PK (Days 1, 55 and 56 only)	x	x[i]			x		x		x	x	x	x	x	x
CCI														
Urine sampling for:														
Urinalysis (and microscopy, as appropriate) (Day -1 only)		x												
On-site urine pregnancy test (females only)[k]	x													

a. Day relative to start of study treatment (Day 1).

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

c. Glucometer measures taken before breakfast on all days while inpatient.
d. Includes blood pressure and pulse rate at all time points.
[redacted]
f. Dosing expected to occur with breakfast (on Day 1) or mixed meal (on Day 56).
g. Meals/snacks to occur on all days while inpatient; identical meals/snacks on Days -1 and 56, and identical snacks on Days -2 and 55.
h. Standard breakfast on Day 1 only.
i. Collection following fasting duration as specified in Section 5.3.1.
[redacted]
k. The test result must be reviewed and deemed acceptable (ie, negative), in order to continue participation in the study.

2. INTRODUCTION

GLP-1 is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake.[1] GLP-1 activation of the GLP-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 the study is to evaluate the safety, tolerability, and PK of multiple oral doses of PF-06882961 in adult Japanese 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 two epicentres (109.6 and 69.2 million of adults with diabetes in 2015).[7] According to National Health and Nutrition Survey in 2016 conducted by Ministry of Health, Labour and Welfare, there is approximately 10 million adults who are expected to be diabetic (HbA1c ≥6.5% or under treatment for diabetes) and 10 million patients are on the verge of becoming diabetic (6.0%≤HbA1c<6.5%). T2DM is characterized by insulin resistance, a disorder in which cells do not respond effectively to insulin, resulting in higher blood glucose levels. Elevated blood glucose levels and increasing severity of insulin resistance result in the need for more insulin over time, eventually resulting in progressive pancreatic β-cell failure.[8] Patients with poorly controlled T2DM have an increased risk of developing complications associated with both microvascular and macrovascular disease, including nephropathy, neuropathy, retinopathy, cardiovascular disease and stroke; and are at 2 to 4 times increased risk of mortality than adults who do not have diabetes.[9] While existing pharmacological options for the treatment of diabetes may provide satisfactory glycemic control for some patients, there remains a large number of patients who do not achieve target glycated hemoglobin (HbA1c) levels, suggesting a need for additional therapeutic options.

Marketed injectable GLP-1R agonists have demonstrated robust glycemic efficacy, weight loss, and cardiovascular safety, with at least one marketed agent demonstrating cardiovascular benefit.[10] Based on the clinical history of injectable, peptidic GLP-1R agonists, an oral, small molecule 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 PD studies demonstrated that, in cells expressing recombinant human and cynomolgus monkey GLP-1R, PF-06882961 dose-dependently promotes 3'-5'-cAMP production. In vivo, PF-06882961 potentiated glucose-stimulated insulin secretion during an IVGTT in cynomolgus monkeys in a dose and concentration dependent manner. 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 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 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 8 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 highest planned clinical dose of PF-06882961, 120 mg BID.

A NOAEL 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 100 mg/kg/day and 150 mg/kg/day（the highest doses administered), 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 EFD, 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 highest anticipated 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 highest anticipated 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 completed dosing with PF-06882961. In C3421001 and C3421003, healthy adult participants were randomized to receive single oral doses of PF-06882961 (or matching placebo). In C3421002, adult participants with T2DM were randomized to receive oral doses of PF-06882961 (or matching placebo) for 28 days, and safety results from this study are provided in Section 2.2.2.1. Refer to the 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.

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,[10,11] 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.

2.2.2.2. Clinical Pharmacokinetics

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

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. Four of the 6 cohorts were titrated for various amounts of time over the 28 days, with a target maximum dose 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 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. 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/1.73 m^2) are not eligible for study entry. Renal function is monitored at each study

	In the clinical trial program only one mild AE (Blood creatinine increased) has been observed in the clinical trial program.	visit by the central 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.
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.
Study Procedures		
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. And, all participants will be monitored for significant hyperglycemia.

2.3.2. Benefit Assessment

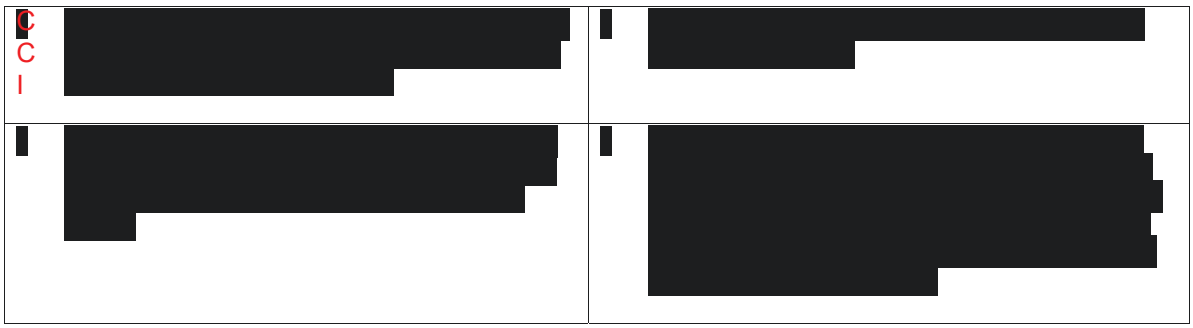
Based on the clinical experience of injectable GLP-1R agonists, a GLP-1R agonist is expected to improve glucose control, reduce HbA1c levels, diminish food intake, and decrease body weight in patients with T2DM. A treatment period of 8 weeks of PF-06882961 in this study has limited clinical benefit to participants with T2DM. This study is designed to generate safety, tolerability, PK CCI data in Japanese T2DM participants for further clinical development.

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety and tolerability of multiple, oral doses of PF-06882961, administered to adult Japanese participants with T2DM.	• Incidence of treatment emergent AEs (AEs and SAEs), clinical laboratory abnormalities, vital signs and ECG parameters during the entire study.
Secondary:	**Secondary:**
• To characterize plasma pharmacokinetics of PF-06882961 following Day 1 and following multiple, oral doses administered to adult Japanese participants with T2DM.	• PF-06882961 plasma pharmacokinetic parameters AUC_{24}, C_{max}, T_{max}, $t_{½}$ (as defined in Section 9.4.3.1, as appropriate for the dosing paradigm) following Day 1, and multiple dose administration, as data permit.
CCI	



4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, double-blind (sponsor-open), placebo-controlled, 4-arm, parallel group study of PF-06882961 in adult Japanese participants with T2DM inadequately controlled on diet and exercise alone.

Participants will receive oral doses of PF-06882961 or placebo in this study. Approximately 9 participants will be enrolled in each arm, for a total of approximately 36 (4 arms) participants randomized. The randomization ratio will be 1:1:1:1 (1 of 3 active dosing regimens of PF-06882961 or placebo), and all 4 arms will be enrolled in parallel. The study will be conducted at a single clinical site in Japan.

Target dose levels, achieved after completion of titration, for the 4 arms of the study are placebo and PF-06882961 doses of 40 mg BID, 80 mg BID, and 120 mg BID. Dose titration will be incorporated to enhance tolerability to PF-06882961.

The maximum dose of PF-06882961 in this study will not exceed 120 mg BID.

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 BID, and up to 2 weeks (The target dose level: 40 mg BID), 4 weeks (The target dose level: 80 mg BID) or 6 weeks (The target dose level: 120 mg BID) of the 8-week dosing duration will be used for dose titration to maximize tolerability of PF-06882961, as depicted in Figure 1 and Table 3. 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.

This study includes a total of 12 visits, of which 2 are inpatient study visits at the site and 7 are outpatient visits excluding screening to the site. The other visits are Follow-up visit and Follow-up telephone contact. Participants will be randomized at V2 to receive PF-06882961 or matching placebo for a duration of 8 weeks, with completion of dosing at V10. The inpatient stays at V2 and V10 consist of 4 days and 3 nights as listed in the SOA. For the study duration between the inpatient study visits, participants will continue dosing with blinded study intervention provided in blister packs, either at home or at an outpatient visit to the study site.

A Follow-up visit and a Follow-up contact (may be a phone call) will occur on V11 (Day 63-70) and on V12 (Day 84-91) following the first dose of study intervention on Day 1, respectively. 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.

The formulation administered in this study will be PF-06882961 tablets, or matching placebo (see Section 6). A study design overview is shown in Section 1.2 and Table 3.

4.2. Scientific Rationale for Study Design

The purpose of this study is to evaluate the safety, tolerability, and PK of multiple oral doses of PF-06882961 in adult Japanese participants with T2DM who are receiving no background anti-hyperglycemic medication. CCI [redacted] Target dose levels, achieved after completion of titration, for the 4 arms of this study are placebo and PF-06882961 doses of 40 mg BID, 80 mg BID, and 120 mg BID. Dosing titration schemes are shown in Table 3.

A baseline day (Day -1) with time-matched procedures will permit an improved assessment of safety, tolerability, CCI [redacted] within participant and placebo-adjusted comparison of dose-response (between participant), as appropriate. The participants and site staff will be blinded to administration of each treatment to permit an unbiased assessment of safety. However, a limited number of members of the Sponsor team will be unblinded to permit review of safety and tolerability while the study is ongoing.

Based on the tolerability data from C3421002, the titration will start at PF-06882961 10 mg BID (or matching placebo), then with increase every week to reach the target dose level of 40 mg BID at the start of Week 3, to reach the target dose level of 80 mg BID at the start of Week 5, and to reach the target dose level of 120 mg BID at the start of Week 7.

All doses will be blinded and consist of 3 tablets administered BID via a blister pack, and dosing regimens will look the same throughout the 8-week dosing duration post randomization.

Clinical safety laboratory tests, assessments of vital signs and 12-lead ECGs, and AE monitoring will provide essential data to evaluate the safety and tolerability of 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 the mean values will be used for analysis at each time point. In addition to triplicate ECG and BP measurements taken prior to dosing of study intervention, triplicate ECG and BP measurements will also be collected at the approximate time to reach C_{max} (T_{max}) on PK sampling days as specified in the SOA to further enhance quantification of any possible drug effect.

As part of the clinical safety laboratory tests, calcitonin, amylase, and lipase will be assessed, as these laboratory parameters have been shown to increase with marketed GLP-1R agonists.[12] 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.

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.

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. [13]

Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.2.1. Study Population

Participants enrolled in this study will have inadequately controlled T2DM (as indicated by HbA1c at screening) on diet and exercise alone. Participants will be allowed to take certain concomitant medications as outlined in Section 6.5.

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, measures will be taken to limit the risk of pregnancy in the female population enrolled (see SOA and Appendix 4).

4.2.2. Pharmacokinetic Parameters

This study will include plasma sampling to examine the Day 1 and steady-state PK of PF-06882961.

CCI [redacted]

CCI [redacted]

4.3. Justification for Dose

4.3.1. Selection of Dose Levels

In this study, PF-06882961 will be administered BID at three dose-levels for 8 weeks. Identical starting dose and weekly titration steps in this study are being utilized in the non-Japanese phase 2 study (C3421005). The dose-titration scheme and the target dose level are shown in Table 3. The PF-06882961 doses selected for this study and the non-Japanese phase 2 study (C3421005) are based on observed safety, tolerability, PK, CCI [redacted] from the non-Japanese phase 1 study (C3421002); as well as the exposure margins relative to completed nonclinical toxicology studies. Exposure margins for the highest proposed dose in this study (120 mg BID) are given in Section 2.2.1.3.

For the high-dose arm, 120 mg BID, the maximum dose in the non-Japanese phase 2 study (C3421005), has been selected to evaluate the safety and tolerability of PF-06882961 in Japanese participants with T2DM so that safety and tolerability can be examined in the dose range including the maximum potential dose in the planned global phase 3 studies.

With regard to the results from the non-Japanese phase 1 study (C3421002), target doses ranging from 10 mg BID to 120 mg BID were generally safe and well tolerated, as described in Section 2.2.2.1. Forty mg BID and 80 mg BID, which are the middle doses in the non-Japanese phase 2 study (C3421005), have been selected as the low-dose and the middle-dose arms, respectively. CCI [redacted]

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), approximately 28 to 35 days post last dose of study intervention.

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. Male and female participants must be 20 to 70 years of age, inclusive, at the time of signing the ICD.

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

Type of Participant and Disease Characteristics:

2. Participants with T2DM who are treated with diet and exercise, and are taking no antidiabetic medications.

3. HbA1c ≥7% 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 logs 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).

- Participants 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. See Section 6.5 for further information on concomitant medications.

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, or a history of ketoacidosis.

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 MTC or MEN2, or participants with suspected MTC per the investigator's judgment.

7. History of acute or chronic pancreatitis.

8. Symptomatic gallbladder disease.

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

10. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HepBsAg, HepBcAb, HCVAb or syphilis. Hepatitis B vaccination is allowed.

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

12. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

13. See Appendix 8 for details regarding prohibited prior/concomitant medications.

Prior/Concurrent Clinical Study Experience:

14. Previous administration with an investigational drug within 4 months or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

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

Diagnostic Assessments:

16. 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.

17. 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.

18. 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.

19. 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 ≥2 × ULN;
    - TBili 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 >1.5 × ULN.
    - Serum calcitonin > ULN.
    - Amylase or lipase > ULN.
    - Fasting blood glucose >270 mg/dL (15.0 mmol/L).

- eGFR <60 mL/min/1.73 m^2 as calculated by the CKD-EPI equation. [14]

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

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 prior to screening.

22. Known or suspected illicit drug use.

23. Blood donation (excluding plasma donations) of approximately 400 mL for the past 3 months or 200 mL for the past 1 month prior to dosing and participants who are planning for blood donation for 3 month after the last dose of study intervention.

24. History of sensitivity to heparin or heparin-induced thrombocytopenia ***only if*** heparin is planned to flush intravenous catheters.

25. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

26. 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 [redacted] the collection of the first blood sample (eg, glucometer measurement, safety laboratory, PK CCI [redacted] assessment) at Screening, each inpatient study day, each outpatient visit, and the follow-up visit.

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

- Noncaffeinated 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 study intervention until collection of the final PK blood sample.

- 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 CRF, however may be submitted to the Sponsor upon request.

- 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 or self-administration of study intervention. ***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.

- Participants will be counseled on appropriate dietary and exercise 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. ***Note***: Participation in formal weight loss programs is prohibited during participation in this study.

5.3.1.1. Admission days (Days -2 and 55)

- The caloric intake/menu assigned to each participant will be based on the Harris Benedict formula (sedentary lifestyle; to be provided to the site prior to study start) using the participant's body weight measured at screening.

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

- A standard breakfast will be provided with dosing at approximately 0800 hours on Day 55 and at approximately the same time on Day -2.

- Lunch will be provided approximately 4 hours after AM dosing (approximately 1200 hours) Day 55 and at approximately the same time on Day -2.

- Dinner will be provided with dosing approximately 10 hours after AM dosing (approximately 1800 hours) Day 55 and at approximately the same time on Day -2.

- An evening snack may be provided at approximately 2200 hours.

    - Participants will receive the same snack each evening prior to the MMTT the following day. Participants will be encouraged to consume the entire evening snack.

5.3.1.2. During inpatient days (Days -1, 1, 56 and 57)

- The caloric intake/menu assigned to each participant will be based on the Harris Benedict formula (sedentary lifestyle; to be provided to the site prior to study start) using the participant's body weight measured at screening.

- On days with MMTT as listed in Table 2 of the SOA (including evening snack prior to MMTT) ***only***: participants will be encouraged to consume all provided food, including the liquid meal and all standard meals provided on these days. In addition, the approximate percentage of food consumed should be recorded in CRF.

    - Participants will not be required to consume all provided food during standard meals on Day 1 and Day 57.

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

- Breakfast will be provided with dosing at approximately 0800 hours each day while inpatient:

    - A standard breakfast will be provided on Day 1 with dosing and Day 57 except when the MMTT is administered;

    - For the MMTT, the mixed meal will be provided as 500 mL of ENSURE® H and will be administered as listed in Table 2 of the SOA. The entire ENSURE® H meal is to be consumed within approximately 10 minutes. (See Section 8.6.1).

- Lunch will be provided approximately 4 hours after AM dosing (approximately 1200 hours). On days with MMTT, lunch will be provided ***after*** the 4-hour postdose blood collection samples for the MMTT have been completed.

- Dinner will be provided approximately 10 hours after AM dosing (approximately 1800 hours).

- An evening snack may be provided at approximately 2200 hours.

- Meals on days with MMTT, will be standardized such that the participants receive the same menus for all meals on these days:

    - Participants will be encouraged to consume their entire meals on Days -1 and 56;

    - If participants do not consume their entire meal on Day -1, they will be instructed to consume the same amount of food (±10%) on the other days with MMTT that they ate on Day -1. If a participant consumes approximately <90% or >110% of what s/he consumed on Day -1 based on visual inspection by the site staff, the approximate percentage consumed should be noted on the source document;

- The start time of all meals will be captured in the CRF on days with MMTT including the ENSURE® H mixed-meal provided for breakfast.

- Participants will be encouraged to eat all standard meals within 30 minutes on days with MMTT administration;

5.3.1.3. Discharge days (Days 2 and 58)

- The caloric intake/menu assigned to each participant will be based on the Harris Benedict formula (sedentary lifestyle; to be provided to the site prior to study start) using the participant's body weight measured at screening.

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

- A standard breakfast will be provided with dosing at approximately 0800 hours each day.

5.3.1.4. Outpatient visit days (Screening, Days 8, 15, 22, 29, 36, 43, 50 and V11 of Follow up visit)

- The caloric intake/menu assigned to each participant will be based on the Harris Benedict formula (sedentary lifestyle; to be provided to the site prior to study start) using the participant's body weight measured at screening.

- 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.

- A standard breakfast will be provided with dosing at approximately the same time each day.

- Lunch will be provided approximately 4 hours after AM dosing (approximately 1200 hours) except on V11 of follow up visit.

5.3.1.5. On Non-visit days and Unscheduled visit

- The study intervention must be administered BID with the morning and evening food, approximately 10-12 hours apart.

5.3.2. Caffeine, Alcohol, and Tobacco

- Caffeine containing products may not be consumed within 2 hours prior to measuring vital signs and ECGs, and may not be consumed on days with MMTT.

- Participants will abstain from alcohol for 24 hours prior to each visit to the site and continue abstaining from alcohol until completion for all procedures of each visit. Except above period, intake of alcohol is permitted in moderation (refer to exclusion criterion 21

for acceptable amount of alcohol consumption). 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 (eg, will not be permitted until after the MMTT procedures), and will not be permitted within 2 hours prior to any vital sign and ECG assessments. 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 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 with food.

PF-06882961 and placebo tablets will be supplied to the site as packaged blister 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	0 mg BID
Route of Administration	Oral	Oral
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) in the morning with food and 3 tablets of study intervention in the evening with food, approximately 10-12 hours apart and at approximately the same time each day. Participants will take a total of 6 tablets of study intervention (PF-06882961 or matching placebo) daily. 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.

Table 3. Titration Scheme and Dosing Level

Target Dose (mg)	Study Week							
	1	2	3	4	5	6	7	8
Placebo	0 mg BID	0 mg BID	0 mg BID	0 mg BID	0 mg BID	0 mg BID	0 mg BID	0 mg BID
40 mg BID	10 mg BID	20 mg BID	40 mg BID	40 mg BID	40 mg BID	40 mg BID	40 mg BID	40 mg BID
80 mg BID	10 mg BID	20 mg BID	40 mg BID	60 mg BID	80 mg BID	80 mg BID	80 mg BID	80 mg BID
120 mg BID	10 mg BID	20 mg BID	40 mg BID	60 mg BID	80 mg BID	100 mg BID	120 mg BID	120 mg BID

6.1.1.1. Inpatient and outpatient visit days

Morning dosing at approximately 0800 hours and evening dosing at approximately 1800 hours will occur with meals at the site on admission and during inpatient days in V2 and V10, except discharge days. For discharge days and outpatient visit days, morning dosing at approximately 0800 hours will occur with meals at the site. Participants will be instructed to arrive at the site in the fasted state for each of the scheduled visits. For V3-V10, participants will be instructed to bring their study intervention supply and dosing diary with them, and to delay self-administration of study intervention on scheduled visit days until 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 is 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 head of the medical institution (where applicable) or study intervention administrator 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

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

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. The participant should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to 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 as summarized in the SOA. Returned study intervention must not be redispensed to the participants.

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

Participants will receive the following number of tablets and corresponding dose level described in Table 4.

Table 4. Dose Levels in Study C3421015

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	-

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

6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and 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 interpretation of the safety, tolerability, PK [redacted] data while the study is ongoing. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. 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 or blinded investigator site personnel 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. 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, sites 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.

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

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are 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

The use of other medications for glycemic control is not permitted in this study (see Appendix 8).

6.5.2. Antihypertensive Medications

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

6.5.3. Lipid Modifying Medications

The use of background lipid modifying agents is permitted unless otherwise noted in Appendix 8. 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 Section 8.2.5.2 and Section 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 6);
- 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.

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See the SOA for data to be collected at the time of discontinuation of study intervention.

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 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.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

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

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, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

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.

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[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 mm Hg 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 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 QTcF intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. When a meal or snack is scheduled at the same time as an ECG, the ECG must be performed prior to the meal/snack.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected at each nominal time point on Day -1 will serve as each 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 QTcF 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 7.

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 central 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 logs 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 logs 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 log.

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

8.2.5.2. 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 central 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 log at each time point specified in the SOA, as well as results reported by the central laboratory, the investigator must assess the glucose values as well as any symptoms documented.

HAE is defined as **one** of the following: [15]

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 central 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 central 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 himself/herself. Neurologic impairment, and not the age of the participant, is the explanation for why the participant could not treat himself/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 central 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 central 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 contact the site and 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 shipped to the central laboratory for analysis).

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

If the results from the central laboratory confirm the readings using glucometer, the participant should 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 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.7. Pregnancy Testing

Pregnancy tests will be both urine and serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in all females at the times listed in the SOA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant’s receiving the 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, except as indicated below, 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 AE or SAE 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 exposes 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 ingestion.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion 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

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

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

Not applicable.

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 of plasma, will be collected into appropriately labeled tubes containing K_2EDTA 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.

The date/time of the blood collection and the date/time of the previous at least ***two*** doses of blinded study intervention prior to **each** of the blood collections related to PK (both pre- *and* post- dose samples) should be noted in a dosing diary (or similar) by the participants and captured in the CRF.

Samples will be used to evaluate the PK of PF-06882961. Samples collected for analyses of PF-06882961 plasma concentration 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 [redacted] These data may not be included in the CSR.

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.

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[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. Statistical Hypotheses

No formal inferential statistics will be applied to the safety, tolerability, PK [redacted] data.

9.2. Sample Size Determination

A sample size of approximately 36 participants (approximately 9 participants in each of the placebo and 3 PF-06882961 arms) has been selected empirically to permit adequate characterization of safety, tolerability, PK [redacted] at each dose level in Japanese participants with T2DM. 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.

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 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.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK concentration	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and in whom at least 1 plasma PK concentration value is reported.
PK parameter	All participants randomly assigned to study intervention who take at least 1 dose of study intervention and who have at least 1 of the PK parameters of interest calculated.
CC [redacted]	[redacted]

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

All treatment arms of PF-06882961 and placebo will be reported separately.

9.4.2. Primary Endpoint(s)

All safety and tolerability analyses will be performed on the safety population.

AEs, ECGs, BP, PR, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study 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 and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be

considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4.2.1. Electrocardiogram Interval Analyses

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

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

Safety QTc Assessment

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

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec.

Changes from baseline will be defined as the change between the postdose QTcF value and the average of the time-matched baseline triplicate values on Day -1.

9.4.3. Secondary Endpoint(s)

9.4.3.1. Pharmacokinetic Analyses of PF-06882961

The PK parameters (AUC_{24}, C_{max}, T_{max}, $t_{½}$) for PF-06882961 following Day 1 and multiple dose administration will be derived from the concentration-time profiles, as data permit. The PK parameters to be assessed in this study, their definition and method of determination are outlined in Table 5. Actual PK sampling times will be used in the derivation of PK parameters. Additional detail on PK parameter definition will be provided in the SAP.

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

The plasma PK parameters will be summarized descriptively by treatment, dose and day, as appropriate.

Table 5. Definition of Plasma PK Parameters for PF-06882961 as Secondary Endpoint

Parameter	Day 1 (D1) or Steady-state (ss)	Definition	Method of Determination
C_{max1} and C_{max2}	D1 & ss	C_{max1}: maximum plasma concentration during the dosing interval τ_1 =0 to 10 hours C_{max2}: maximum plasma concentration during the dosing interval τ_2=10 to 24 hours	Observed directly from data
C_{max}	D1 & ss	Maximum plasma concentration observed from time zero to 24 hours	Observed directly from data
T_{max}, T_{max1} and T_{max2}	D1 & ss	Time for C_{max}, C_{max1} and C_{max2}	Observed directly from data as time of first occurrence
AUC_{24}	D1 & ss	Area under the plasma concentration-time profile from time zero to time 24 hours	$AUC_{\tau1}$ +$AUC_{\tau2}$
$t_{½}$	ss	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.

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[redacted]

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CCI [redacted]

CCI [redacted]

9.4.5. Other Safety Analyses

9.4.5.1. Hypoglycemia Monitoring and Reporting

The HAEs will be listed in a separate table and summarized categorically.

CCI [redacted]

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, CCI [redacted] and/or supporting clinical development.

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 head of the medical institution 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 or authorized site personnel 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 or authorized site personnel 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 or authorized site personnel 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 study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

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 study team on demand system.

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

Table 7. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine eGFR **Plasma** glucose 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	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
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT (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, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).

Investigators must document their review of each laboratory safety report.

After randomization, the investigator site and other blinded personnel will be blinded to plasma glucose obtained after the first dose of study intervention measured by the central laboratory, unless the FPG meets the criterion for hypo-or hyper-glycemia as listed in Section 8.2.5.2 and Section 8.2.5.3.

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

10.3.1. Definition of AE

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

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. 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 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 <u>not</u> 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 old 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.

*) Not approved in Japan.

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.

*) Not approved in Japan.

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).

*) Not approved in Japan.

CCI [redacted]

[redacted]

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- [redacted]
- [redacted]

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

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as 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.

10.7. Appendix 7: 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 participants 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 participants 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.

10.8. Appendix 8: Prohibited Prior/Concomitant Medications

The following medications are prohibited until the first follow-up visit (ie, Visit 11, Week 9-10), unless stated otherwise. If a participant receives a prohibited medication, the investigator should contact the Sponsor Clinician or Sponsor Medical Monitor to determine if the participant may remain in the study.

Drug Classes and/or Drugs	**Timeframe of Restriction Prior to Screening Visit**
Thiazolidinediones such as pioglitazone.	90 days
Subcutaneously administered agents for glycemic control (eg, insulin, exenatide, liraglutide, dulaglutide). ***Note***: Short-term (ie, ≤7 days) of insulin administration is permitted if participant is hospitalized.	90 days
Pharmacological agents with approved indication for weight loss such as mazindol.	90 days
Oral anti-diabetic medications, including: Biguanides such as metformin, buformin. Sulfonylureas such as acetohexamide, chlorpropamide, glyclopyramide, glibenclamide, gliclazide, glimepiride. Meglitinide analogues such as repaglinide, nateglinide, mitiglinide. DPP-4i such as sitagliptin, alogliptin, saxagliptin, linagliptin, vildagliptin, teneligliptin, anagliptin, trelagliptin, omrigliptin. α glucosidase inhibitors such as acarbose, voglibose, miglitol. SGLT2 inhibitors such as ipragliflozin, luseogliflozin, tofogliflozin, canagliflozin, empagliflozin, dapagliflozin. Anti-hyperglycemic medications, including bromocriptine.	60 days
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.	60 days
Immunosuppressants such as cyclosporine and tacrolimus.	60 days
Appetite or weight modifying medications, including nonprescription or herbals.	60 days
Anti-psychotic medications such as olanzapine, risperidone.	60 days
Coumarin type anticoagulants or other anticoagulants (eg, dabigatran).	60 days
Anticonvulsants if prescribed for seizure disorder.	60 days
Antiarrhythmic medications whose primary mechanism of action is sodium or potassium channel blockade (eg, procainamide, quinidine, proprafenone; as well as amiodarone, sotalol).	60 days

Drug Classes and/or Drugs	**Timeframe of Restriction Prior to Screening Visit**
Note: β-adrenergic receptor blocking agents (eg, atenolol, metoprolol) and calcium channel blockers (eg, diltiazem, amlodipine, nifedipine) are permitted.	
Sympathomimetic agents. ***Note***: Inhaled β-adrenergic receptor agonists (eg, albuterol) are permitted.	60 days
BCRP Substrates Rosuvastatin. ***Note***: Other statins are permitted. Sulfasalazine	Prohibited post randomization
Use of CYP3A4/5 substrates with narrow therapeutic index – eg, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus.	Prohibited post randomization
Use of agents which are potent inducers of CYP3A (eg, rifampin).	Prohibited for 2 weeks before randomization and post randomization
Use of agents which are clinically significant OATP inhibitors (eg, cyclosporine, rifampin).	Prohibited post randomization
Use of potent 3A4 inhibitors	Prohibited post randomization
Paclitaxel, torsemide.	Prohibited post randomization

10.9. Appendix 9: Proposed Chronology of Procedures

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

- 12-lead ECG: obtain prior to blood samples, and prior to dosing (except for post-dose collection) (see Section 8.2.4);
- Vital Signs (BP, PR): obtain prior to obtaining blood samples and prior to dosing (except for post-dose collection) (see Section 8.2.3);
- Fasting blood samples (for safety [see Section 8.2.6], PK [see Section 8.5], CCI [redacted] CCI [redacted] after assessment of 12-lead ECG and vital signs but prior to dosing (If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments [PR and BP] should be collected prior to the insertion of the catheter.);
- C CCI [redacted]
- Post-dose PK blood collection to occur approximately 4 hours post-dose (see Section 8.5): if collection time coincides with time of a meal/snack, these blood samples should be collected just prior to the meal/snack;
- Other pre-dose procedures: obtain sample/perform procedure as close as possible to the scheduled time, but may be obtained before or after blood sample collection(s);
- Dosing: must occur in the morning with food and in the evening with food; and where applicable, after any pre-dose blood sample collection(s).

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
%CV	percent coefficients of variance
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AV	atrioventricular
BCRP	breast cancer resistance protein
β-hCG	β-human chorionic gonadotropin
BID	twice a day
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
CL	total clearance of drug from eg, plasma
CCI [redacted]	[redacted]
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
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

Abbreviation	Term
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]	[redacted]
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
HAE	hypoglycemic adverse event
HbA1c	hemoglobin A1c
HCVAb	hepatitis C antibody
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
CCI [redacted]	[redacted]
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IND	Investigational New Drug
INR	international normalized ratio
IP Manual	investigational product manual
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
K_2EDTA	dipotassium edetic acid (ethylenediaminetetraacetic acid)
LBBB	left bundle branch block

Abbreviation	Term
LFT	liver function test
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
CCI	[redacted]
MDR1	multidrug resistance mutation
MEN2	multiple endocrine neoplasia syndrome type 2
MMTT	mixed-meal tolerance test
msec	millisecond
MTC	medullary thyroid carcinoma
N/A	not applicable
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PD	pharmacodynamic(s)
pH	potential of hydrogen
PI	principal investigator
PK	pharmacokinetic(s)
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction/complex
QTc	corrected QT interval
QTcF	corrected QT using Fridericia's formula
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGLT2	sodium glucose cotransporter 2
SOA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
ss	steady-state
SSID	single subject identifier
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Terminal phase half-life
T2DM	type 2 diabetes mellitus
TBA	total bile acids
TBili	total bilirubin

Abbreviation	Term
TEAE	treatment-emergent adverse event
T_{max}	time to reach C_{max}
TSH	thyroid stimulating hormone
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	woman of childbearing potential

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