A PHASE 1, OPEN-LABEL, SINGLE-DOSE, PARALLEL GROUP STUDY TO EVALUATE THE PHARMACOKINETICS OF PF-06882961 IN PARTICIPANTS WITH TYPE 2 DIABETES MELLITUS WITH VARYING DEGREES OF RENAL IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT RENAL IMPAIRMENT

Investigational Product Number:	PF-06882961
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI
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Short Title: Pharmacokinetic Study of PF-06882961 in Participants With Type 2 Diabetes Mellitus With Varying Degrees of Renal Impairment and Participants Without Renal Impairment

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	13 October 2020	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: Pharmacokinetic Study of PF-06882961 in Participants With Type 2 Diabetes Mellitus With Varying Degrees of Renal Impairment and in Participants Without Renal Impairment.

Rationale

The purpose of this multi-site, Phase 1, open-label, parallel-group study is to characterize the effect of varying degrees of renal impairment on the pharmacokinetics (PK), safety and tolerability of a single oral dose of PF-06882961 in participants with type 2 diabetes mellitus (T2DM), compared with participants with normal renal function.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To compare the PK of PF-06882961 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to T2DM participants without renal impairment.	• Plasma: C_{max}, AUC_{inf}, AUC_{last}, fu, as data permit.
Secondary:	**Secondary:**
• To compare additional PK parameters of PF-06882961 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to T2DM participants without renal impairment.	• Plasma: $C_{max,u}$, $AUC_{inf,u}$, $AUC_{last,u}$, CL/F, CL_u/F, V_z/F, $V_{z,u}$/F, T_{max}, $t_{1/2}$, as data permit.
• To evaluate the safety and tolerability of a single oral dose of PF-06882961 in T2DM participants with varying degrees of renal impairment and in participants with normal renal function.	• Incidence and severity of treatment-emergent AEs, clinical laboratory abnormalities, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG) parameters (heart rate, QT, QTcF, PR and QRS intervals).
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To compare urine PK parameters of PF-06882961 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to T2DM participants without renal impairment.	• Urine: CL_r, Ae_{24}, Ae_{24}%.
• To compare the PK of PF-06882961 following administration of a single oral dose in adult participants with T2DM and normal renal function relative to healthy participants with normal renal function.	• Plasma: C_{max}, T_{max}, AUC_{inf}, AUC_{last}, CL/F, V_z/F, $t_{1/2}$, fu, as data permit; • Urine: CL_r, Ae_{24}, Ae_{24}%.

• To explore the relationship of markers of innate organic anion transporting polypeptide (OATP) activity in adult participants with T2DM and varying degrees of renal impairment relative to participants with normal renal function.	• Coproporphyrin I (CP-I) concentration.
• To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.	• Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).

Overall Design

This Phase 1, open-label, single-dose, parallel group, multi-site study will assess the effect of varying degrees of renal impairment on the PK, safety and tolerability of PF-06882961 after a single oral dose of 20 mg administered in a fed state (Section 5.3.1).

Number of Participants

Approximately 40 participants will be enrolled in the study. All participants assigned to investigational product (IP) and who take at least 1 dose of IP will be evaluable. Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and sponsor.

Intervention Groups and Duration

Participants with T2DM and varying degrees of renal impairment (Group 3: T2DM with mild renal impairment, Group 4: T2DM with moderate renal impairment, Group 5: T2DM with severe renal impairment) will be recruited and enrolled first. An average value for age and weight for these groups will be determined and participants in Groups 1-2 (Group 1: healthy with normal renal function, Group 2: T2DM with normal renal function) will be recruited last to match the average demographics (at a minimum, age and weight, and, as much as practically possible, gender) across the pooled Groups 3-5. Approval from the sponsor must be garnered **before** proceeding with dosing participants in Groups 1 and 2. All participants will receive a single oral dose of IP in the fed state.

Screening will occur within 28 days of the first dose of study medication. All participants will provide informed consent and undergo Screening evaluations to determine their eligibility. For individual participants, the total duration of participation from the Screening Visit to the Follow-up Contact will be a minimum of approximately 5 weeks and a maximum of approximately 10 weeks.

Data Monitoring Committee: No

Statistical Methods

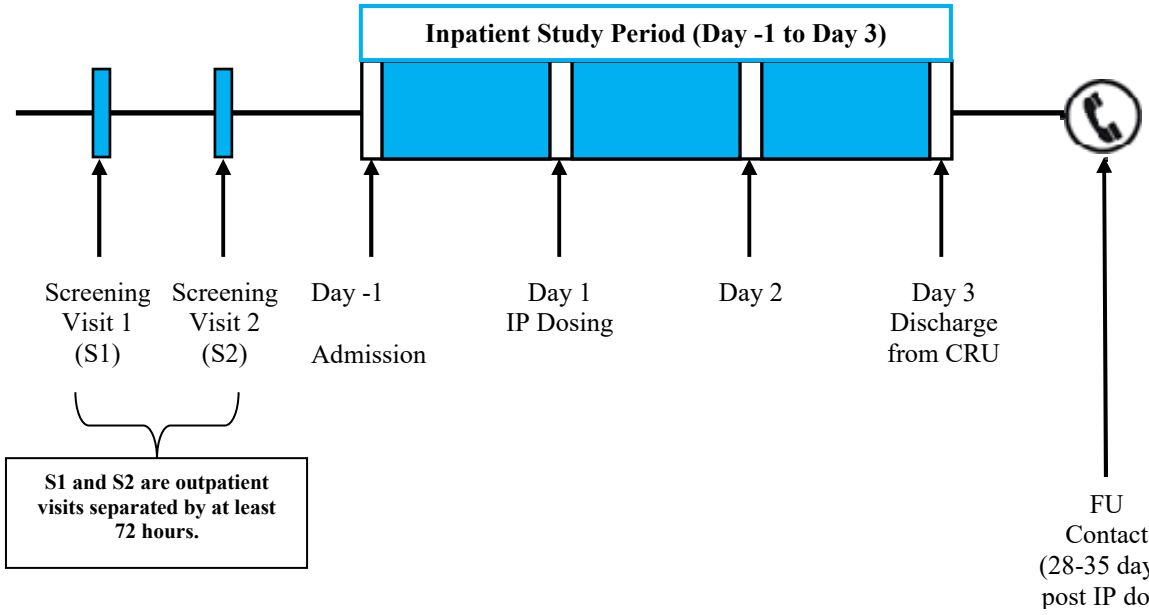
Linear regression will be used to characterize the potential relationship between appropriate PK parameters (CL/F, CL_u/F and CL_r) for PF-06882961 and renal function (eGFR).

A one-way analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{inf} (if data permit), AUC_{last}, C_{max} and fu of PF-06882961 for each of the T2DM renal impairment groups (Test, Groups 3, 4, 5) to the T2DM normal renal function group (Reference, Group 2). Also, the T2DM normal renal function group (Test, Group 2) will be compared to the healthy normal renal function group (Reference, Group 1). The ANOVA model will include all groups (ie, both T2DM and healthy participants from the 5 groups). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and corresponding 90% CIs. If substantial differences in demographic characteristics between healthy (Group 1), T2DM normal (Group 2) and T2DM renal impairment function participants (Groups 3, 4, 5) are observed, covariates such as weight and age may be explored.

The PK parameters for PF-06882961 will also be summarized descriptively by renal function group and population (healthy vs. T2DM).

For summary statistics and median/mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

1.2. Schema



*Screening period is ≤28 days from dosing on Day 1.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to STUDY ASSESSMENTS AND PROCEDURES Section 8.2 of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier (for proposed chronology of procedures refer to Appendix 9; for abbreviations refer to Appendix 10)	**Screening**		**Study Period**																**Follow-up[b]**	**ET**
	S1[a]	**S2[a]**																		
Study Day	**≤-28**		**-1**	**1**												**2**		**3**	**28-35**	
Hours Post Dose	**--**	**--**	**--**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**16**	**24**	**36**	**48**			
Informed consent & demography	X																			
Adverse event monitoring	X	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Outpatient visit	X	X																	X[b]	X
COVID-19 symptoms and risk assessment	X		X																	
COVID-19 testing	X[c]																			X
Inpatient stay at Clinical Research Unit			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X		
Eligibility assessment	X		X																	
Medical history	X		X																	
Alcohol/tobacco & contraception use	X		X																	
Review contraception use (females only)	X		X																X	
Prior/concomitant treatments	X		X																X	
Physical exam (height and body weight at S1, ***only***)[d]	X		X															X		X
Alcohol breath test[e]	X		X																	
Single, *supine* 12-lead ECG	X			X														X		X
Single, *seated* vital sign assessment[f]	X		X[g]	X											X			X		X
Glucometer measurement[h]				X											X			X		X
Standard meals[i]			X	X				X				X			X			X		
Investigational product administration[j]				X[j]																
Blood Sampling for:																				
Safety laboratory tests - after ≥8-hr fast (incl. eGFR)[k,l]	X	X[l]		X														X		X
Serum FSH (females only), HbA1C, C-peptide	X																			
Serum pregnancy test (WOCBP only)[l,m]	X	X		X																X
CCI [redacted]				CCI																
Exploratory plasma for coproporphyrin-I				X																
PF-06882961 PK				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PF-06882961 unbound fraction for protein binding				X				X												

Visit Identifier (for proposed chronology of procedures refer to Appendix 9; for abbreviations refer to Appendix 10)	Screening		Study Period															Follow-up[b]	ET
	S1[a]	S2[a]																	
Study Day	≤-28		-1	1												2		3	28-35	
Hours Post Dose	--	--	--	0	1	2	3	4	5	6	8	10	12	16	24	36	48		
Urine Sampling for:																			
Urine drug test[o]	X																		
Urinalysis (and microscopy, if needed)[p]	X			X													X		X
On-site pregnancy test (WOCBP ***only***)[m]			X																
PF-06882961 PK[q]				X	→	→	→	→	→	X	→	→	X	→	X				

a. Screening visits S1 and S2 should be separated by at least 72 hours. S2 is optional only for participants with dialysis.

b. Visit to be performed as telephone contact and must occur 28 to 35 days from administration of the final dose of investigational product. A clinic visit may be performed in place of telephone contact, if deemed necessary by the investigator.

c. COVID-19 viral test to occur between Day -5 and Day -2 to permit availability of test result prior to admission on Day -1.

d. Full physical examination (PE) will be performed at Screening visit S1; at all other time points, a brief physical examination is performed and may be performed at non-specified visits if there are findings during the previous exam or new/open AEs, if appropriate and at investigator discretion.

e. Alcohol breath test may be conducted at investigator discretion.

f. Includes blood pressure, temperature and pulse rate.

g. On Day -1, only temperature is required on admission.

h. Glucometer measures will be taken before breakfast in participants with T2DM on all days while inpatient. Additional measurements may be made at the discretion of the investigator.

i. Meals/snacks will occur on all days while inpatient as per Section 5.3.1. While inpatient, mealtimes should match nominal time of approximately 0H, 4H, 10H relative to dosing on Day 1.

j. Dosing will occur within approximately 10 minutes of completion of breakfast on Day 1.

k. The eGFR determination will be performed by the central lab.

l. Only serum creatinine and eGFR (along with pregnancy testing) should be collected at S2.

m. Test result must be reviewed and deemed acceptable (ie, negative) to continue participation in the study. For a participant on dialysis who is anuric only, an alternative method (eg, blood) for urine pregnancy testing may be used.

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o. For a participant on dialysis who is anuric only, an alternative method (eg, saliva) for drug testing may be used.

p. For a participant on dialysis who is anuric only, urinalysis is not required to be collected.

q. Blank pre-dose urine sample to be collected within 24H prior to dosing and urine should be collected at intervals of 0-6, 6-12 and 12-24 hours after dosing. If participant is on dialysis and has no urine output, no urine PK sample will be collected.

2. INTRODUCTION

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

2.1. Study Rationale

The purpose of this multi-site, Phase 1, open-label, parallel-group study is to characterize the effect of varying degrees of renal impairment on the PK, safety and tolerability of a single oral dose of PF-06882961 in participants with T2DM, compared with participants with normal renal function.

2.2. Background

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

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

2.2.1. Nonclinical Pharmacology

In vitro primary pharmacodynamics (PD) studies demonstrated that, in cells expressing recombinant human and cynomolgus monkey GLP-1R, PF-06882961 dose-dependently promotes 3'-5'-cyclic adenosine monophosphate (cAMP) production. In vivo, PF-06882961 potentiated glucose-stimulated insulin secretion during an intravenous glucose tolerance test (IVGTT) in cynomolgus monkeys in a dose and concentration dependent manner. 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 Investigator's Brochure (IB) for more details on the nonclinical pharmacology of PF-06882961.

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2.2.3. 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 no observed adverse effect level (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.

Embryo-fetal developmental studies were completed in rats and rabbits. Based on the lack of maternal toxicity or adverse effects on embryo-fetal development, the NOAEL for maternal and developmental toxicity in rats was 500 mg/kg/day (highest dose evaluated). In embryo-fetal studies conducted in rabbits, the NOAEL for maternal and developmental toxicity was 250 mg/kg/day.

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.

2.2.4. Clinical Overview

Three clinical studies, C3421001, C3421002 and C3421003 have completed dosing with PF-06882961. In C3421001 and C3421003, single oral doses of PF-06882961 up to 300 mg (or matching placebo) were generally safe and well tolerated in healthy adult participants. In the multiple dose study C3421002, PF-06882961 doses up to 120 mg BID (or matching placebo) for 28 days were generally safe and well-tolerated in adult participants with T2DM on a background of metformin therapy, and safety results from this study are provided in Section 2.2.4.1. Refer to the IB for more details on these studies and the known drug class effects of marketed injectable GLP-1R agonists.

2.2.4.1. Clinical Safety

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

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 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 all-causality treatment-emergent adverse events (TEAEs) were reported in these participants, of which a majority (294 or 92%) were mild in intensity, 23 (or 7%) were moderate, and 2 (or 1%) were severe in intensity.

The total number of TEAEs generally increased with higher daily doses of PF-06882961. The most frequently reported TEAEs (by number of occurrences) in these cohorts have been nausea (48), dyspepsia (32), vomiting (26), diarrhea (24), headache (23), constipation (20), and decreased appetite (19). In addition, there was one symptomatic hypoglycemic AE reported in 1 participant in the 120 mg BID group. This AE was non-fasting, mild in severity, and of limited duration (15 minutes). No deaths occurred in the C3421002 study. Two 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. One participant experienced 2 non-treatment-related SAEs, 1 of which occurred in the follow-up period and the other occurred outside of the study reporting period.

In C3421002, there were isolated values for laboratory tests, vital signs and ECG intervals outside of the reference ranges; however, no clear adverse trends were apparent in these parameters. As has been reported for marketed GLP-1R agonists[11] increases in heart rate were observed, with mean increases ranging from 5 to 15 beats per minute (bpm) across doses administered, and with most heart rate values within the normal range.

2.2.4.2. Clinical Pharmacokinetics

The clinical PK of PF-06882961 in healthy adult participants have been evaluated in 3 completed studies: C3421001, C3421002 and C3421003. The results of these completed studies are summarized in the PF-06882961 IB.

In study C3421001, following a single, oral dose administration of PF-06882961 to healthy participants at doses ranging from 3 mg to 300 mg under fasted conditions, median T_{max} ranged from 2.0 to 6.0 hours post dose. Mean $t_{½}$ values ranged from 4.3 to 6.1 hours. Plasma exposure, as assessed by dose-normalized geometric mean AUC_{inf} and C_{max} values, appeared to increase in a dose proportional manner across the 3 mg to 300 mg doses. Variability in PF-06882961 exposure based on geometric percent coefficient of variation (%CV) ranged from 50% to 91% for C_{max} and 28% to 60% for AUC_{inf} across the 3 mg to 300 mg dose range.

In study C3421002, following 28 days of dosing to participants with T2DM, accumulation was modest for the BID IR formulation treatments, with mean ratios based on dose normalized AUC_{24} (R_{ac}) values ranging from 1.203-2.009. Day 28 plasma exposure as measured by geometric mean AUC_{24} values appeared to increase in an approximate dose proportional manner across all IR treatments. Urinary recovery of PF-06882961 was low, with <0.1% of the dose recovered unchanged in urine on Day 28. Mean $t_{½}$ values on Day 28 across all treatments ranged between 4.681 to 8.090 hours, and no apparent trends were observed across various treatments, regimens, or doses administered. Inter-participant variability for PF-06882961 exposure was based on geometric mean was 31%-87% for AUC_{24} and 32%-94% for C_{max} and on Day 28 across all treatments and cohorts. CCI

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2.3. Benefit/Risk Assessment

A single dose of PF-06882961 administered in this study is not expected to provide any clinical benefit to healthy participants or T2DM participants with or without renal impairment. This study is designed primarily to characterize the effect of varying degrees of renal impairment on the PK of PF-06882961. Results from this study will be used in conjunction with collective safety, efficacy, and PK/PD data from other PF-06882961 studies to provide recommendations on dosing for participants with varying degrees of renal impairment.

In line with the clinical profile of marketed GLP-1R agonists,[12-14] the most frequently reported AEs with PF-06882961 administration have been nausea, diarrhea, dyspepsia, headache, and vomiting. In addition, as has been reported for marketed GLP-1R agonists, increases in heart rate have been observed with PF-06882961 administration, with most heart rate values within the normal range. Based on current Phase 1 data with PF-06882961, a 20 mg dose is anticipated to be well tolerated, even if plasma concentrations are higher with renal impairment.

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

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To compare the PK of PF-06882961 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to T2DM participants without renal impairment.	• Plasma: C_{max}, AUC_{inf}, AUC_{last}, fu, as data permit.
Secondary:	**Secondary:**
• To compare additional PK parameters of PF-06882961 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to T2DM participants without renal impairment.	• Plasma: $C_{max,u}$, $AUC_{inf,u}$, $AUC_{last,u}$, CL/F, CL_u/F, V_z/F, $V_{z,u}$/F, T_{max}, $t_{1/2}$, as data permit.
• To evaluate the safety and tolerability of a single oral dose of PF-06882961 in T2DM participants with varying degrees of renal impairment and in participants with normal renal function.	• Incidence and severity of treatment-emergent AEs, clinical laboratory abnormalities, vital signs (blood pressure and pulse rate), ECG parameters (heart rate, QT, QTcF, PR and QRS intervals).
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To compare urine PK parameters of PF-06882961 following administration of a single oral dose in adult participants with T2DM and varying degrees of renal impairment relative to T2DM participants without renal impairment.	• Urine: CL_r, Ae_{24}, Ae_{24}%.
• To compare the PK of PF-06882961 following administration of a single oral dose in adult participants with T2DM and normal renal function relative to healthy participants with normal renal function.	• Plasma: C_{max}, T_{max}, AUC_{inf}, AUC_{last}, CL/F, V_z/F, $t_{1/2}$, fu, as data permit; • Urine: CL_r, Ae_{24}, Ae_{24}%.
• To explore the relationship of markers of innate OATP activity in adult participants with T2DM and varying degrees of renal impairment relative to participants with normal renal function.	• CP-I concentration.
• To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.	• Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).

4. STUDY DESIGN

4.1. Overall Design

This Phase 1, open-label, single-dose, parallel group, multi-site study will assess the effect of varying degrees of renal impairment on the PK, safety and tolerability of PF-06882961 after a single oral dose of 20 mg administered in a fed state (Section 5.3.1).

Approximately 40 participants will be enrolled in the study. Refer to Table 1 below for details of study groups. Due to the potential difficulty in recruiting T2DM patients with estimated glomerular filtration rate (eGFR) <30 mL/min, the number of participants to be enrolled in this group is flexible (6 to 8 participants).

This study will permit enrollment of 2-4 participants on dialysis, as part of the severe renal impairment group, to assist in recruitment of patients with more advanced renal impairment and to permit assessment of the PK of PF-06882961 in participants with the highest degree of renal impairment. CCI [redacted] CCI [redacted] dialysis is not expected to significantly impact the clearance of PF-06882961 and therefore the dialysis clearance of PF-06882961 will not be characterized in this study. Thus, Day 1 (per the SoA) will occur in dialysis patients on a day in which dialysis is ***not*** administered.

Table 1. Study Groups

Group	Disease State	Renal Impairment	No. of Participants	eGFR[a] (mL/min)
1	None (healthy)	None (Normal Renal Function)	8	≥90
2	T2DM	None (Normal Renal Function)	8	≥90
3	T2DM	Mild	8	60-89
4	T2DM	Moderate	8	30-59
5	T2DM	Severe	6-8[b]	<30

a. Estimate of eGFR based on the SCr-based CKD-Epi equation. The eGFR will be multiplied by each participant's ratio of BSA/1.73 to obtain the BSA-unnormalized eGFR value. The average of the 2 unnormalized eGFR values from S1 and S2 will be used for study enrollment and group placement. ***Note:*** participants on dialysis will be placed in Group 5 regardless of unnormalized eGFR from S1 and S2.

b. This includes approximately 4 participants not on dialysis and 2-4 participants on dialysis.

Screening will occur within 28 days of the first dose of study intervention on Day 1. All participants will provide informed consent and undergo Screening evaluations to determine their eligibility. All participants who are not on dialysis must have stable renal function to enter the study, defined as ≤25% difference between 2 measurements of BSA-unnormalized eGFR obtained from the 2 screening visits, S1 and S2 as listed in the SoA.

As indicated in Table 1, the estimate of eGFR will be based on the SCr-based CKD-Epi equation:[15]

- eGFR (mL/min/1.73m^2) = 141 × min (SCr /κ, 1)$^{\alpha}$ × max(SCr /κ, 1$^{)-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if Black].

where:

- SCr is serum creatinine in mg/dL (based on the standardized assay);
- κ is 0.7 for females and 0.9 for males;
- α is -0.329 for females and -0.411 for males;
- Min indicates the minimum of SCr /κ or 1;
- Max indicates the maximum of SCr /κ or 1;
- Age is in years.

The eGFR value will be multiplied by each participant's ratio of BSA/1.73 to obtain the BSA-unnormalized eGFR value as shown below:

- eGFR (mL/min) = eGFR (mL/min/1.73m^2) * [BSA (m^2) / 1.73].

The BSA of an individual will be calculated using the following equation:[16]

BSA (m^2) = [Weight(kg)$^{0.425}$ × Height(cm)$^{0.725}$] × 0.007184

Participants with T2DM and varying degrees of renal impairment (Groups 3-5) will be recruited and enrolled first. An average value for age and weight for these groups will be determined and participants in Groups 1-2 will be recruited to match the average demographics (at a minimum, age and weight, and as much as practically possible gender) across the pooled Groups 3-5. Recruitment for participants in Groups 1-2 may start when approximately 75% of total participants across Groups 3-5 (ie, approximately 17-18) have been dosed. Approval from the sponsor must be garnered ***before*** proceeding with dosing participants in Groups 1 and 2.

Refer to Section 1.2 for study schema. For individual participants, the total duration of participation from the Screening Visit to the Follow-up Contact will be a minimum of approximately 5 weeks and a maximum of approximately 10 weeks.

Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and sponsor.

4.2. Scientific Rationale for Study Design

The purpose of this study is to characterize the effect of varying degrees of renal impairment on the PK, safety and tolerability of PF-06882961. PF-06882961 is an oral GLP-1R agonist that is currently being investigated as chronic therapy to improve glycemic control in adult participants with T2DM. Chronic kidney disease (CKD) occurs in 20-40% of patients with diabetes and may be present at the time of diagnosis of T2DM.[17]

Renal impairment can affect drug metabolism and transport in other organs (such as the liver), which may lead to clinically relevant changes in non-renal clearance (where OATP substrates may be affected).[18-20] Based on this, and since patients with T2DM may experience varying stages of CKD, a full-range study design including participants with no, mild, moderate and severe renal impairment (including participants requiring dialysis) will be conducted. Consistent with the recommendation in the draft FDA Guidance for Industry "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labelling"[21] that the participants should be representative of a typical patient population, T2DM participants will be the primary population. Healthy participants with normal renal function will be enrolled to enable comparison of PK parameters between the age, weight, and gender of healthy participants, T2DM participants with varying degrees of renal impairment, and T2DM participants with normal renal function. CCI [redacted] CCI [redacted] CCI [redacted] Therefore, to compare exposures directly in this study, both T2DM and healthy participants with normal renal function are included. Renal impairment classification will be based on the eGFR according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation which has been used in renal outcome studies.[22,23,24]

Based on the draft FDA Guidance for Industry, plasma and urine samples will be analyzed for PF-06882961. As PF-06882961 was observed to have a $t_{½}$ of approximately 4-8 hours, plasma sampling up to 48 hours will be collected. Since PF-06882961 is highly protein bound, to assess the in vivo protein binding of PF-06882961 with varying degrees of renal impairment, the fraction unbound (fu) of PF-06882961 will be determined at approximately the expected T_{max} in each participant. To explore the relationship between OATP activity and CKD, the endogenous biomarker, coproporphyrin I (CP-I), will be measured prior to dosing. CP-I has been reported to be a potential marker of OATP activity. In this study, a single dose of PF-06882961 will be administered with a standard breakfast to reflect the conditions for anticipated use of PF-06882961 in the target T2DM population. Additionally, in study C3421001 in healthy participants, variability based on geometric %CV for C_{max} was lower following administration with a high-fat meal (23% in the fed state, compared to 91% in the fasted state). The adjusted geometric mean C_{max} was 57% lower (90% CI: 28%, 74%) in the fed state compared to the fasted state, while mean AUC_{inf} values were similar (approximately 12% lower in the fed state [90% CI: -5%, 26%]).

While GLP-1R agonists typically are not associated with hypoglycemia unless co-administered with anti-diabetic agents that can cause hypoglycemia (such as insulin or sulfonylureas), blood glucose concentrations will be monitored throughout the study via glucometer, and monitoring of symptomatic HAEs will be performed. As is typical for studies with renally impaired participants, vital signs will be obtained in the seated position. In addition, COVID-19 specific assessments have been incorporated to minimize the risks of COVID-19 related complications to participants and the study site personnel.

Both females of childbearing potential as well as those who are of non-childbearing potential will be enrolled given the availability of embryo fetal developmental (EFD) toxicity studies with PF-06882961. However, as marketed GLP-1R agonists are listed as contraindicated in pregnancy, measures will be taken to limit the risk of pregnancy in the female population enrolled (see SoA and Section 10.4).

The potential risk of exposure to PF-06882961 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[25]

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4.3. Justification for Dose

Based on data available from the completed C3421001 study, a single dose of PF-06882961 20 mg is expected to be safe and well tolerated and will provide data to meet the objectives of this study. This dose selection also takes into account safety considerations for patients with varying degrees of renal impairment in whom an increase in plasma concentration of PF-06882961 may be observed in this study. Based on current Phase 1 data, a 20 mg dose is anticipated to be well tolerated, even if exposures are approximately 2-fold higher with renal impairment and approximately 1.7-fold higher in T2DM versus healthy participants. Additionally, a 20 mg dose will allow for adequate characterization of the plasma PK profile out to 48 hours and therefore it is suggested to choose the highest single dose that is anticipated to be well tolerated (ie, 20 mg). Since the exposure of PF-06882961 is approximately dose-proportional over the range of clinical doses (up to single dose of 300 mg and up to 120 mg BID), the results of this study can be extrapolated to understand the effect of renal impairment on the PK of PF-06882961 over the range of clinical doses planned for future studies.

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 last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the trial.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

5.1.1. Inclusion Criteria for All Participants

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

1. Stable renal function (for participants not on dialysis) defined as ≤25% difference between 2 measurements of eGFR (as calculated by the sponsor-identified central laboratory using the CKD-EPI equation)[1] obtained at Screening visits S1 and S2. The average of the 2 eGFR values obtained from S1 and S2 will be used for study enrollment and assignment to appropriate renal function group (see Table 1). ***Note:*** participants on dialysis will be placed in Group 5 regardless of eGFR from S1 and S2 (S2 is optional for dialysis participants only).

Age and Sex:

2. Male and female participants must be ≥18 years of age, inclusive, at the time of signing the informed consent document (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:

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

Weight:

4. Body mass index (BMI) of ≥18.0 kg/m^2 and <45.4 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.1.2. Additional Inclusion Criteria for Healthy Participants with Normal Renal Function (Group 1)

1. No clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate measurement, standard 12-lead ECG and clinical laboratory tests.

2. Normal renal function (mean eGFR ≥90 mL/min) based on an average of measures from Screening visits S1 and S2.

3. Demographically comparable to participants with impaired renal function:

   a. A body weight within ±15 kg of the mean body weight of the pooled renal impairment groups (Groups 3, 4, and 5), as provided by sponsor;

   b. An age within ±10 years of the mean age of the pooled renal impairment groups (Groups 3, 4 and 5), as provided by sponsor;

   c. Attempts will be made to ensure that the male to female distribution in Group 1 is comparable to that in the pooled renal impairment groups (Cohorts 3, 4, and 5).

5.1.3. Additional Inclusion Criteria for T2DM Participants with Normal Renal Function (Group 2)

1. A prior diagnosis of T2DM with an HbA1c ≥6% and ≤10.5%, at Screening visit S1, confirmed by a single repeat, if deemed necessary.

2. Normal renal function (mean eGFR ≥90 mL/min) based on an average of measures from Screening visits S1 and S2.

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

4. Demographically comparable to participants with impaired renal function:

   a. A body weight within ±15 kg of the mean body weight of the pooled renal impairment groups (Groups 3, 4, and 5), as provided by sponsor;

b. An age within ±10 years of the mean age of the pooled renal impairment groups (Groups 3, 4, and 5), as provided by sponsor;

c. Attempts will be made to ensure that the male to female distribution in Group 2 is comparable to that in the pooled renal impairment groups (Cohorts 3, 4, and 5).

5.1.4. Additional Inclusion Criteria for T2DM Participants with Impaired Renal Function (Groups 3-5)

1. A prior diagnosis of T2DM with an HbA1c ≥6% and ≤10.5%, at Screening visit S1, confirmed by a single repeat, if deemed necessary.

2. Meet the eGFR criteria listed for Groups 3, 4, or 5 (for participants not on dialysis) in Table 1 based on an average of measures from Screening visits S1 and S2.

3. Stable concomitant medications, as defined in Section 6.5, for the management of medical conditions relevant to an individual participant's medical history. Participants receiving fluctuating concomitant medications/treatments may be considered, ***on a case-by-case basis*** with input from sponsor, if the underlying disease is stable.

4. For Group 5 participants on dialysis **only**, participants must have required hemodialysis for at least 6 weeks and need dialysis sessions 3 times per week.

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria for All Participants

Participants in all 5 Groups are excluded from the study if any of the following criteria apply:

Medical Conditions:

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

2. Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, or any area of intestinal resection, active inflammatory bowel disease or pancreatic insufficiency). *NOTE*: subjects who have undergone cholecystectomy and/or appendectomy are eligible for this study so long as the surgery occurred more than 6 months prior to Screening;

3. 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.

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

5. History of chronic or acute pancreatitis within 5 years.

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

7. History of diabetic ketoacidosis.

8. History of myocardial infarction, unstable angina, arterial revascularization, stroke, New York Heart Association Functional Class II-IV heart failure, or transient ischemic attack within 3 months of Screening visit S1.

9. Urinary incontinence.

10. Participants with acute renal disease.

11. Renal allograft recipients.

12. Participants with other clinically significant disease, in the judgment of the investigator that may affect the safety of the participant or that may affect the PK of PF-06882961. See Section 6.5 for further information.

Prior/Concomitant Therapy:

13. See Appendix 8 (Section 10.8) for details regarding prohibited prior/concomitant medications.

Prior/Concurrent Clinical Study Experience:

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

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

Diagnostic Assessments:

16. Screening standard 12-lead ECG that demonstrates a clinically relevant abnormality that requires further diagnostic evaluation or intervention (eg, new, clinically relevant arrhythmia, conduction disturbance, findings suggestive of ischemia). A potential participant whose pre-dose ECG (on Day 1, 0 hour) demonstrates a clinically relevant abnormality that requires further diagnostic evaluation or intervention will be considered a screen failure.

17. A positive COVID-19 test in the screening period.

18. A positive urine drug test (or other type of drug test in anuric participants on dialysis only).

    - ***Note:*** Participants who have been medically prescribed opiates/opioids, benzodiazepines or marijuana and report the use of these drugs to the investigator at Screening may be eligible to participate with sponsor approval. Use of marijuana during inpatient stay is prohibited.

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

    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level ≥2 × upper limit of normal (ULN);
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.
    - Fasting C-peptide <0.8 ng/mL.
    - Fasting plasma glucose (FPG) >270 mg/dL (15 mmol/L) at screening (S1).

Other Exclusions:

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

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

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

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

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

5.2.2. Additional Exclusion Criteria for Healthy Participants with Normal Renal Function (Group 1)

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including clinically relevant and significant drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).

2. Use of prescription or non-prescription drugs and dietary and herbal supplements within 14 days or 5 half-lives (whichever is longer) prior to the first dose of IP (Refer to Section 6.5 for additional details). As an exception, ibuprofen or acetaminophen may be used at doses of ≤1 g/day. Limited use of non-prescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

3. Screening seated systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg, following at least 5 minutes of supine rest. If SBP is >140 mmHg or DBP >90 mmHg, the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

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

   - HbA1c ≥6.0% at Screening visit S1;
   - FPG ≥126 mg/dL at screening (S1);
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level ≥1.5 × upper limit of normal (ULN).

5.2.3. Additional Exclusion Criteria for T2DM Participants with Normal Renal Function (Group 2)

1. At Screening, seated systolic blood pressure (SBP) ≥160 mm Hg and/or diastolic blood pressure (DBP) ≥105 mm Hg after ≥5minute of seated rest, with a single repeat permitted to assess eligibility, if needed, at each of these 2 visits.

5.2.4. Additional Exclusion Criteria for T2DM Participants with Impaired Renal Function (Groups 3-5) ***only***

1. At Screening, persistent severe, uncontrolled hypertension; for example: ***seated*** systolic blood pressure (SBP) ≥180 mm Hg and/or diastolic blood pressure (DBP) ≥105 mm Hg after ≥5minute of seated rest, with a single repeat permitted to assess eligibility, if needed, at each of these 2 visits:

- For subjects with SBP ≥160 mm Hg **or** DBP ≥100 mm Hg, the period between Screening and Day 1 must be used to refine the doses of the agents used for management of blood pressure with the aim to have stable BP on Day 1 (See Section 5.2.5).

2. For participants in Group 5 on Dialysis only: Hemodynamic instability during or at the conclusion of dialysis during the 2 weeks prior to dosing, as marked by symptomatic hypotension.

5.2.5. Criteria for Dosing on Day 1

Participants will progress to dosing on Day 1 provided they have satisfied all the following criteria:

- In women of childbearing potential, urine pregnancy test on Day -1 is negative;
- Cohort 1 and Cohort 2 only: Approval from the sponsor must be obtained before proceeding with dosing participants in either Cohort 1 or Cohort 2;
- Cohorts 2-5 only: Participants must have measurement on Day 1 of SBP <160 mm Hg and DBP <100 mm Hg;
    - A single repeat assessment is permitted, to confirm that the above criterion is met [and in such cases, the repeat assessment overrides initial results].

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

While inpatient, the meals consumed are expected to follow the restrictions outlined below:

- Participants must abstain from all food and drink (except water) for at least 8 hours prior to scheduled safety laboratory and the predose PK evaluations.

Dose administered in the fed state on Day 1:

- Water may be consumed as desired (ad libitum).
- After collection of predose safety and PK samples on Day 1, participants should begin consumption of a standard breakfast approximately 30 minutes prior to oral PF-06882961 administration. The breakfast will be consumed over approximately a 20 minute period, with the IP administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to complete the entire breakfast.

- Lunch will be provided approximately 4 hours after oral dosing of PF-06882961. Dinner will be provided approximately 10 hours after oral dosing of PF-06882961.

- An evening snack may be permitted.

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

- Participants will refrain from consuming red wine, grapefruit, or grapefruit related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of IP until collection of the final PK blood sample.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. Caffeine, Alcohol, and Tobacco

- Caffeine containing products will be permitted during the study with the following restrictions: caffeine containing products may not be consumed within 2 hours prior to measuring vital signs and ECGs.

- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test at the discretion of the investigator. Alcohol breath test will be considered source data and will not be required to be reported.

- Tobacco and nicotine use may be allowed according to CRU practices. Tobacco/nicotine use will not be permitted during frequent sampling procedures and will not be permitted within 2 hours prior to any vital sign or ECG assessments. Tobacco/nicotine use will also not be permitted 2 hours before and 2 hours following any dose of IP.

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 a female participant has selected an appropriate method of contraception (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 entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

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

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

6. STUDY INTERVENTION

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

For the purposes of this protocol, the term investigational product (IP) may be used synonymously with study intervention.

6.1. Study Intervention Administered

For this study, the IP is PF-06882961.

PF-06882961 will be supplied by Pfizer as 10 mg tablets in bulk along with individual dosing containers, as necessary, for unit dosing.

6.1.1. Administration

Participants will receive IP at approximately 0800 hours (plus or minus 2 hours). Details on meals and dietary requirements and activity restrictions on the day of dosing (Day 1) are given in Section 5.3.

Investigator site personnel will administer IP with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the IP whole, and will not manipulate or chew the IP prior to swallowing.

6.2. Preparation/Handling/Storage/Accountability

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

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

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an IP accountability form/record.

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

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

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

7. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer on discovery. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

6.2.1. Preparation and Dispensing

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

Tablets will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

This is a non-randomized, open-label study. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. The first 4 digits of the SSID will reflect the sponsor assigned site number and the remaining 4 digits will reflect each participants' unique number assigned in chronological order of when informed consent is obtained.

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

Healthy participants will abstain from all concomitant medications, except for the treatment of AEs, as described in Section 5.2.2 of this protocol.

Participants with T2DM will be allowed to be on certain concomitant medications that have been prescribed. Any concomitant medications may be administered in the morning if they can be administered under fed conditions or may be administered at 2 hours after IP administration. On all other study days, participants are to receive their background

medications at their usual times. Attempts should be made not to alter the doses and regimens of any concomitant medications after enrollment 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.

In addition, T2DM participants using insulin are permitted to have sliding scale insulin or dose adjustment in insulin while confined to the CRU to attempt to maintain fasting and post prandial glucose readings at similar levels that are achieved at home and based on the calories consumed while confined in the CRU.

Phosphate binders, antacids, and bile acid binding resins (eg, cholestyramine, colestipol) must not be administered within 8 hours before dosing to 4 hours after dosing.

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

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

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).

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-06882961. Standard medical supportive care must be provided to manage the AEs, including administration of carbohydrates to treat HAEs (see Section 8.2.6).

6.6. Dose Modification

Dose modification of PF-06882961 is not allowed.

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

Not applicable as this is a single dose study.

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 termination visit applies only to participants who received IP 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.

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

8. STUDY ASSESSMENTS AND PROCEDURES

Participants will be screened within 28 days prior to administration of the IP to confirm that they meet the study population criteria for the study. The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

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

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

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

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

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

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

The total blood sampling volume for individual participants in this study is approximately 90 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

Not Applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete 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.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

8.2.2. Vital Signs

Vital signs (systolic BP, diastolic BP, temperature and pulse rate) will occur as specified in the SoA. Seated BP will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mmHg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

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.

8.2.2.1. Temperature

Body temperature will be measured at the timepoints listed in the SoA. No eating, drinking, or smoking is allowed for 15 minutes prior to this measurement.

8.2.3. Electrocardiograms

Standard 12-Lead ECGs should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures 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.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If 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 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 Section 10.7.

8.2.4. Clinical Safety Laboratory Assessments

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

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

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

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

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

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive IP.

8.2.5. Glucometer Monitoring of Glucose

Investigators will monitor fingerstick blood glucose (FSBG) using glucometer measurements in participants with T2DM at the times specified in the Schedule of Activities. FSBG measurements should be taken before breakfast while the participant is confined to the CRU.

FSBG readings will be maintained at the sites in source documents, and only the glucose results from the laboratory will be reported in the study database.

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

8.2.6. Management of Hypoglycemia

Any episode of hypoglycemia must be captured on the HAE CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.2.6.1 below.

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

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

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

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

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

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 intravenous (IV) glucose.

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

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

1. The participant exhibits altered mental and/or physical functioning that requires assistance from another person for recovery.

2. The participants exhibit at least 1 of the following neurological symptoms:

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

3. Either:

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

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

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

8.2.7. Management of Hyperglycemia

Hyperglycemia is defined as the following:

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

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 collection procedures should be reinforced with the participant.

A participant with hyperglycemia should receive treatment at the discretion of the investigator (see Section 6.5).

8.2.8. 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 WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening (S1 and S2), appropriate contraception must be commenced/continued and a second negative pregnancy test result will be required prior the participant's receiving the IP. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by Institutional Review Boards (IRBs)/ethics committees (ECs) or if required by local regulations.

8.2.9. COVID-19 Specific Assessments

Participants will be pre-screened for COVID-19 related symptoms and risks[26,27] and tested for SARS-CoV-2 infection using a locally approved test at the timepoints specified in the SoA. Additional testing may be conducted as required by local regulations or by the Principal Investigator. Results must be negative for admission to the CRU.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving 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 are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for Suspected Unexpected Serious Adverse Reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

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

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

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

8.3.5.2. Exposure During Breastfeeding

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. 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

This section is not applicable because efficacy is not expected in the study population.

8.3.9. Medical Device Deficiencies

Not Applicable.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of PF-06882961 greater than 120 mg within a 24-hour time period (±2 hours) will be considered an overdose.

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

In the event of an overdose, the 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 study intervention (whichever is longer).

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

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

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

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

8.5.1. Plasma for Analysis of PF-06882961

Blood samples of approximately 3 mL, to provide a minimum of plasma volume 1 mL, will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (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 (eg, within 6 minutes of a 60-minute sample) 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 data collection tool (eg, 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 data collection tool (eg, 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, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. 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 standard operating procedures (SOPs).

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

8.5.2. Plasma for Determination of PF-06882961 Unbound Fraction

During the study, a blood sample (approximately 12 mL) to provide sufficient plasma for unbound fraction determination will be collected into an appropriately labeled tube containing K_2EDTA as defined in the SoA.

8.5.3. Urine for Analysis of PF-06882961

One aliquot of approximately 2 mL urine sample is needed for the analysis of PF-06882961.

Urine will be collected at times specified in the SoA (but no urine will be collected for anuric dialysis participants).

- ***Prior to*** dosing on Day 1, each participant must complete a forced void with an aliquot (approximately 10 mL) from this urine (urine blank) labeled and stored frozen for measurement of drug concentrations, per detailed instructions offered in a laboratory manual prior to the start of the study.

- ***Following*** dosing on Day 1, each void post dose will be collected and saved in a container and stored in refrigerated conditions (ie, 2-8°C) for the duration of the collection interval, as specified in the SoA.

    - At the end of the collection interval, participants must complete a forced void with this complete void included as part of the interval collection;

    - The urine container will be mixed thoroughly and total volume plus weight of the urine collected during the interval recorded.

Details regarding the processing, storage and shipping of the samples will be provided in the lab manual. Samples collected for urine analyses of PF-06882961 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, or for other internal

exploratory purposes. The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study. The urine samples must be processed as indicated to maintain sample integrity. Any deviations from the urine sample processing steps given in the protocol or lab manual, including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation. Samples for analysis of PF-06882961 PK will be analyzed using validated analytical methods in compliance with Pfizer SOPs.

8.6. Pharmacodynamics

PD parameters are not evaluated in this study.

8.7. Pharmacogenomics

Pharmacogenomics (specified analysis) are not evaluated in this study.

8.8. Biomarkers

Collection of a sample for biomarker research is also part of this study.

8.8.1. Exploratory Biomarker for Measurement of CP-I

A blood sample (approximately 4 mL) to provide sufficient plasma will be collected as defined in the SoA. This sample may be used for other exploratory biomarker studies, unless prohibited by local regulations or an ethics committee (EC) decision.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

No formal statistical hypothesis testing will be performed in this study.

9.2. Sample Size Determination

Approximately 8 participants will be enrolled into each of the 5 groups (healthy normal, T2DM normal, T2DM mild, T2DM moderate and T2DM severe). This is an estimation study and the sample size is based on the recommendation from the EMA in "Guideline on the evaluation of the PK of medicinal products in patients with decreased renal function"[28] and is consistent with the draft FDA Guidance for Industry "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labelling".[21]

A sample size of 8 participants per group will provide 90% confidence intervals (CIs) for the difference between groups of ±0.490 on the natural logarithm scale for AUC_{inf} (or C_{max}) with 80% coverage probability. The expected widths of the 90% CIs with 80% coverage probability for the comparisons of each of the T2DM renal impaired groups (Groups 3, 4, 5) to the T2DM normal group (Group 2) and the comparison of the T2DM normal group (Group 2) to the healthy normal group (Group 1) are shown in Table 2 for a range of possible effects.

Table 2. Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects

Estimated Effect (Test/Reference)	AUC_{inf} or C_{max}	
	Probable 90% CI	Probable CI Width
75%	(46%, 122%)	76%
100%	(61%, 163%)	102%
150%	(92%, 245%)	153%
200%	(123%, 326%)	203%
400%	(245%, 653%)	408%

These estimates are based on an assumed conservative standard deviation of 0.489 (equivalent to a geometric coefficient of variation of 52%) for both $\log_e AUC_{inf}$ and $\log_e C_{max}$ based on data from the first in human study in healthy volunteers (C3421001) and preliminary data from the multiple ascending dose study in T2DM (C3421002).

Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and sponsor.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Evaluable	All participants assigned to IP and who take at least 1 dose of IP.
Safety	All participants assigned to IP and who take at least 1 dose of IP.
PK Concentration Set	The PK concentration population is defined as all participants who received at least 1 dose of PF-06882961 and in whom at least 1 plasma concentration value is reported.
PK Parameter Set	The PK parameter analysis population is defined as all participants who received at least 1 dose of PF-06882961 and have at least 1 of the PK parameters of interest calculated.

9.4. Statistical Analyses

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

9.4.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination 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. COVID-19 specific assessments data will be considered source data and will not be required to be reported.

9.4.2.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

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

9.4.3. Other Analyses

Pharmacogenomic (PGx) data will be collected and retained for future analyses, but will not be analyzed, specifically, for this study.

9.4.3.1. Pharmacokinetic Analyses

9.4.3.1.1. Analysis Populations

The analysis populations are defined as in Section 9.3.

9.4.3.1.2. Derivation of Pharmacokinetic Parameters Prior to Analysis

9.4.3.1.2.1. Plasma

The plasma PK parameters for PF-06882961 following single dose administration will be derived from the concentration time profiles as detailed in Table 3. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 3. Plasma PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
AUC_{inf*}	Area under the plasma concentration-time profile from time zero extrapolated to infinite time.	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last*} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum observed concentration.	Observed directly from data.
T_{max}	Time to maximum observed concentration.	Observed directly from data as time of first occurrence.
$t_{1/2}$*	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.
CL/F*	Apparent clearance.	$Dose/AUC_{inf}$.
V_z/F*	Apparent volume of distribution.	$Dose/(AUC_{inf}*k_{el})$.
fu	Fraction of unbound drug in plasma.	Cu/C (where Cu represents unbound concentration and C represents total concentration).
$AUC_{last,u}$	Unbound area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration.	$fu*AUC_{last}$.
$AUC_{inf,u}$	Unbound area under the plasma concentration-time profile from time zero extrapolated to infinite time.	$fu*AUC_{inf}$.
$C_{max,u}$	Maximum observed concentration of unbound drug.	$fu*C_{max}$.
CL_u/F	Apparent clearance of unbound drug.	$Dose/(AUC_{inf,u})$.
$V_{z,u}$/F	Apparent volume of distribution of unbound drug.	$Dose/(AUC_{inf,u}*k_{el})$.

* as data permit.

9.4.3.1.2.2. Urine

The following urine PK parameters will be calculated for PF-06882961 (Table 4):

Table 4. Urine PK Parameters

Parameter	Definition	Method of Determination
Ae_{24}	Total amount of unchanged drug excreted in the urine over 24 hours.	Sum of amount excreted for each collection period.
Ae_{24}%	Total amount of unchanged drug excreted in the urine over 24 hours, expressed as percent of dose.	100*(Ae_{24}/Dose).
CL_r	Renal clearance.	Ae_{24}/AUC_{24}.

9.4.3.1.3. Statistical Methods

Linear regression will be used to characterize the potential relationship between appropriate PK parameters (CL/F, CL_u/F and CL_r) for PF-06882961 and renal function (eGFR). eGFR values obtained on Day 1 and only participants from the T2DM groups (Groups 2 to 5) will be included in the regression analysis. Estimates of the slope and intercept, together with their precision (90% CIs), and the coefficient of determination will be obtained from the model. The effect of covariates such as weight, gender, and age may be explored, and details will be provided in the SAP.

A one-way analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{inf} (if data permit), AUC_{last}, C_{max}, fu, $AUC_{inf,u}$ (if data permit), $AUC_{last,u}$ and $C_{max,u}$ of PF-06882961 for each of the T2DM renal impairment groups (Test, Groups 3, 4, 5) to the T2DM normal renal function group (Reference, Group 2). Also, the T2DM normal renal function group (Test, Group 2) will be compared to the healthy normal renal group (Reference, Group 1). The ANOVA model will include all groups (ie, both T2DM and healthy participants from the 5 groups). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and corresponding 90% CIs. If substantial differences in demographic characteristics between healthy (Group 1), T2DM normal (Group 2) and T2DM renal impairment function participants (Groups 3, 4, 5) are observed, covariates such as weight, gender, and age may be explored.

The PK parameters for PF-06882961 will also be summarized descriptively by renal function group and population (healthy vs. T2DM). Box and whisker plots for individual PK parameters (AUC_{inf}, AUC_{last}, C_{max}, fu, $AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$) will be constructed by renal function group and population and overlaid with geometric means.

For summary statistics and median or mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

Plots of PK parameters (CL/F, CL_u/F and CL_r) for PF-06882961 versus renal function (eGFR as obtained on Day 1) will be constructed. A regression line and 90% confidence region for the PK parameters and eGFR will be included if appropriate. Vertical lines for the renal function group cut-off values will also be presented on the plots. Different symbols will be used to identify participants from different renal function groups.

Consistent with the draft FDA Guidance for Industry,[21,18] relevant tables and figures may be generated based on eGFR calculated using the Cockcroft-Gault or the Modification of Diet in Renal Disease (MDRD) formulas as described in the SAP.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development.

9.5.1. Data Monitoring Committee

This study will not use a Data Monitoring Committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

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

10.1.8. Study and Site Closure

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

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

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

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and IP identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. 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 safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 5. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea Creatinine eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) Magnesium Phosphate AST ALT Total bilirubin GGT Alkaline phosphatase Uric acid Albumin Total protein Amylase Lipase	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	• Serum and Urine Pregnancy test (β-hCG)[d] • COVID-19 test At screening only: • HbA1c • Serum FSH[b] • C-peptide • Urine drug screening[c]
Additional Tests[e]			
AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR			

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. At screening (S1) and in females only.
c. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific). Participants may undergo random drug testing at the discretion of the investigator. For a participant on dialysis who is anuric only, an alternative method (eg, saliva) for drug testing may be used.
d. Serum and urine pregnancy testing for all women of childbearing potential (WOCBP); urine pregnancy testing to be done on-site using kits provided by sponsor-identified central laboratory. For a participant on dialysis who is anuric only, an alternative method (eg, blood) for urine pregnancy testing may be used.
e. Additional testing only for the management of participants with elevated liver enzymes as outlined in Appendix 6.

Investigators must document their review of each laboratory safety report.

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

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

10.3.1. Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of

the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct

normal life functions.

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

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

AE and SAE Recording/Reporting

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

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

terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

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

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

Assessment of Intensity

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

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

Assessment of Causality

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

reporting requirements.

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

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) 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 and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

  OR

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

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

10.4.3. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

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

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

2. Postmenopausal female.

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

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

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

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

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

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

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.

Collection of Pregnancy Information

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

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

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

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

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

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

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular complexes (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 (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and

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

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

ECG Findings That Qualify as 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 follow-up visit (ie, 28-35 days after the last dose), 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 should be included in the study.

Drug Classes and/or Drugs	**Timeframe of Restriction**
GLP-1R agonists.	90 days prior to Screening Visit S1
DPP-4 inhibitors, pramlintide, repaglinide.	Screening Visit (S1) to Follow Up visit
Systemic glucocorticoids such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone. ***Note***: As an exception, steroid-containing inhalers, nasal sprays and topical formulations are permitted.	Screening Visit (S1) to Follow Up visit
Immunosuppressants such as cyclosporine and tacrolimus.	Screening Visit (S1) to Follow Up visit
Rosuvastatin. ***Note***: Other statins are permitted.	Day 1 (day of dosing)
Sulfasalazine (sensitive BCRP substrate)	Day 1 (day of dosing)
Use of chronic agents which are clinically significant OATP inhibitors (eg, cyclosporine, gemfibrozil, rifampin).	Screening Visit (S1) o Follow Up visit
Use of chronic agents which are potent inducers of CYP3A (eg, rifampin, phenytoin, carbamazepine, phenobarbital).	Screening Visit (S1) to Follow Up visit
Use of potent CYP3A4 inhibitors (eg, ritonavir, indinavir, itraconazole, clarithromycin).	Screening Visit (S1) to Follow Up visit
Use of moderate CYP3A4 inducers (eg, efavirenz, lopinavir, elagolix).	Screening Visit (S1) to Follow Up visit
Use of moderate CYP3A4 inhibitors (eg, diltiazem, verapamil, erythromycin, fluconazole).	Screening Visit (S1) to Follow Up visit

10.9. Appendix 9: Proposed Chronology of Procedures

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

- 12-lead ECG: obtain prior to vital signs assessment, blood samples, and prior to dosing (except for post-dose collection) (see Section 8.2.3);
- Vital Signs (BP, PR, temperature): obtain after 12-lead ECG collection but prior to obtaining blood samples and prior to dosing (except for post-dose collection) (see Section 8.2.2);
- Fasting blood samples [for safety (see Section 8.2.7), PK (see Section 8.5), exploratory biomarkers (see Section 8.8) and banked biospecimens (see Section 8.7.1)]: after assessment of 12-lead ECG and vital signs but prior to dosing;
- For the random, post dose PK blood collection to occur approximately 2 to 6 hours post dose (see Section 8.5): if collection time coincides with time of a meal/snack, these blood samples should be collected just prior to the meal/snack;
- Other pre-dose procedures: obtain sample/perform procedure as close as possible to the scheduled time, but may be obtained before or after blood sample collection(s);
- Dosing: must occur with the morning meal; 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.

	Term
Abs	absolute
AE	adverse event
Ae_{24}	total amount of unchanged drug excreted in the urine over 24 hours
Ae_{24}%	total amount of unchanged drug excreted in the urine over 24 hours, expressed as percent of dose
ALT	alanine aminotransferase
AM	Morning
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC_{24}	area under the plasma concentration-time profile from time 0 to time 24 hours
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
$AUC_{inf,u}$	unbound area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}).
$AUC_{last,u}$	unbound area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
AV	Atrioventricular
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CL_u/F	apparent clearance of unbound drug after oral administration
CL_r	renal clearance

	Term
CL/F	apparent clearance
C_{max}	maximum observed concentration
$C_{max,u}$	maximum observed concentration of unbound drug
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CP-I	coproporphyrin I
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
%CV	percent coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DPP	Dipeptidyl Peptidase
DDI	drug-drug interactions
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EFD	embryo fetal developmental
EMA	European Medicines Agency
eGFR	estimated glomerular filtration rate
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSBG	fingerstick blood glucose
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
fu	fraction of unbound drug in plasma
FU	follow up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
H or h or hr	hour
HAE	hypoglycemic adverse event

	Term
HbA1c	glycated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IP manual	investigational product manual
IR	immediate release
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVGTT	intravenous glucose tolerance test
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
Log_e	natural logarithm
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MDR1	multidrug resistance mutation
MEN2	multiple endocrine neoplasia syndrome type 2
mg/kg	milligrams per kilogram
msec	millisecond
MTC	medullary thyroid carcinoma
N/A	not applicable
NOAEL	no-observed-adverse-effect level
OATP	organic anion transporting polypeptides
OCT2	organic cation transporter 2
PCD	primary completion date
PD	pharmacodynamic(s)
PE	physical examination
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PR	ECG parameter/interval
PT	prothrombin time
PVC	premature ventricular contraction/complex
QRS	ECG parameter/interval

	Term
QT	time from the beginning of the QRS complex to the end of the T wave
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
R_{ac}	accumulation ratio
RBC	red blood cell
RNA	ribonucleic acid
S1	screening visit 1
S2	screening visit 2
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SCr	serum creatinine
SMP	study monitoring plan
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SSID	Single Subject Identifier
ST	slow titration
SToD	study team on demand
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal phase half-life
TBili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to maximum observed concentration
T2DM	type 2 diabetes mellitus
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
Vz/F	apparent volume of distribution
$Vz_{,u}/F$	Unbound Vz/F
WBC	white blood cell
WOCBP	woman of childbearing potential

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