A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, SINGLE-DOSE, PARALLEL COHORT STUDY TO COMPARE THE PHARMACOKINETICS OF PF-06882961 IN ADULT PARTICIPANTS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT HEPATIC IMPAIRMENT

Study Intervention Number:	PF-06882961
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Short Title: Pharmacokinetic Study of PF-06882961 in Participants With and Without Varying Degrees of Hepatic Impairment

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original Protocol	05 October 2020	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: Pharmacokinetic Study of PF-06882961 in Participants With and Without Varying Degrees of Hepatic Iimpairment.

Rationale

The primary purpose of this non-randomized, open-label study is to characterize the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics (PK) of PF-06882961 following administration of a single oral dose of PF-06882961.

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 varying degrees of hepatic impairment relative to age- and body weight-matched participants without hepatic impairment.	• Plasma: C_{max}, AUC_{inf}, AUC_{last}, fu as data permit.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of a single oral dose of PF-06882961 when administered to adult participants with varying degrees of hepatic impairment and in age- and body weight-matched participants without hepatic impairment.	• Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To compare additional PK parameters of PF-06882961 following administration of a single oral dose in adult participants with varying degrees of hepatic impairment and in age- and body weight-matched participants without hepatic 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.

Overall Design

This is a non-randomized, open-label, single-dose, parallel-cohort, multicenter study to investigate the effect of varying degrees of hepatic function on the plasma PK of PF-06882961 after a single, oral 20 mg dose administered in the fed state. Safety and tolerability will be evaluated throughout the study.

Number of Participants

Approximately 24 participants will be enrolled to study intervention such that approximately 24 evaluable participants complete the study.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process.

Intervention Groups and Duration

A total of approximately 24 participants with varying degrees of hepatic function will be administered a single, oral 20 mg dose of PF-06882961 in the fed state as shown in the table below.

Hepatic Function Categories Based on Child Pugh-Score

Cohort	Description	Child-Pugh Score	Number of Participants
1	Without hepatic impairment	Not Applicable	6[a]
2	Mild hepatic impairment	Class A (5 to 6 points)	6
3	Moderate hepatic impairment	Class B (7 to 9 points)	6
4	Severe hepatic impairment	Class C (10 to 15 points)	6[b]

a. Additional participants may be dosed to a maximum of 8 participants to ensure mean age ±5 years and mean body weight ±10 kg of this cohort is aligned with the pooled average assessed when ≥75% of participants are dosed across the other 3 cohorts.

b. If recruitment across the sites selected proves to be prohibitive, study will dose only 4 participants in this cohort.

Categorization of participants into Cohort 2-4, inclusive, will be done based on Child-Pugh scores determined, as described in Appendix 8, at the screening visit. Participants will be dosed in a staged manner such that those with moderate and severe hepatic impairment (Cohorts 3 and 4) will be evaluated first followed by participants with mild hepatic impairment (Cohort 2). Participants without hepatic impairment (Cohort 1) will be recruited near the end of the study to match the average demographics (at a minimum, age and weight; and gender as much as practically possible) across the pooled Cohorts 2 through 4.

Approval from the sponsor must be obtained before proceeding with recruitment for participants on Cohort 1 or Cohort 2.

For individual participants, the total duration of participation from the screening visit to the follow-up visit will range from approximately 5 weeks (minimum) to approximately 9 weeks (maximum).

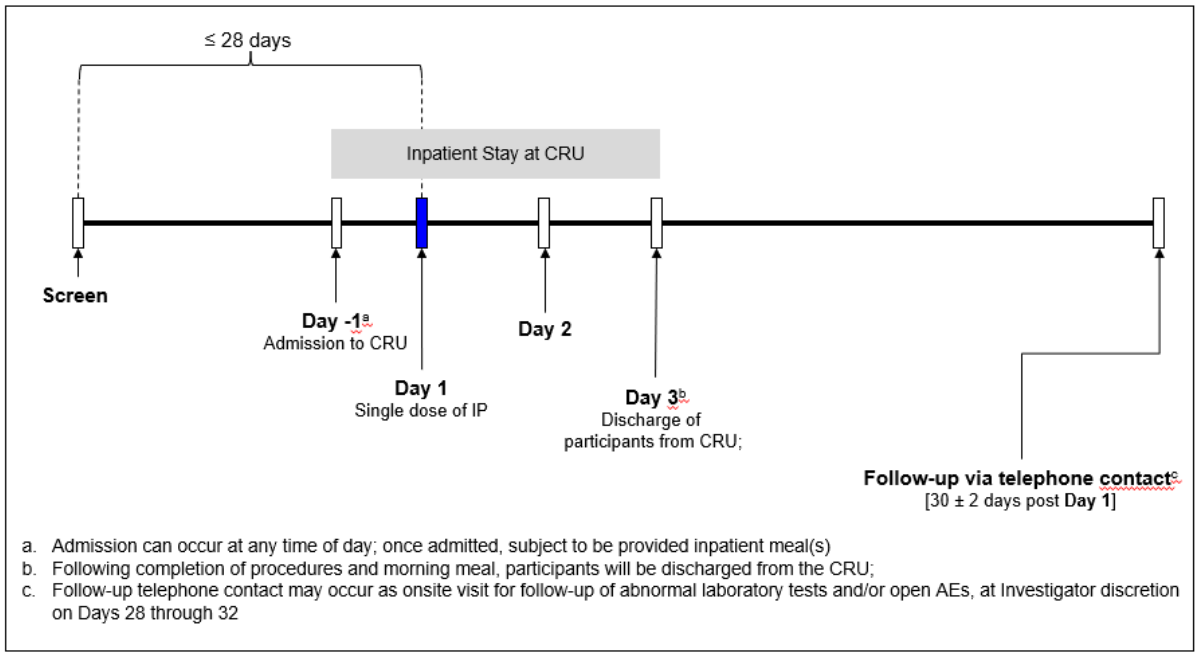
Data Monitoring Committee or Other Independent Oversight Committee

A data monitoring committee or independent oversight committee will not be utilized.

Statistical Methods

The effect of varying degrees of hepatic impairment on PK parameters will be assessed by constructing 90% confidence intervals (CI) around the estimated difference between each of the Test (hepatic impaired) cohorts and the Reference (without hepatic impairment) cohort. A 1-way analysis of variance (ANOVA) will be used to compare the natural log transformed PF-06882961 AUC_{inf}, C_{max}, AUC_{last}, and fraction unbound (fu), as data permit, for each of the hepatic impairment cohorts (Test) to the cohort without hepatic impairment (Reference). Estimates of the adjusted mean differences (Test - Reference), and corresponding 90% CIs, will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

1.2. Schema



a. Admission can occur at any time of day; once admitted, subject to be provided inpatient meal(s)
b. Following completion of procedures and morning meal, participants will be discharged from the CRU;
c. Follow-up telephone contact may occur as onsite visit for follow-up of abnormal laboratory tests and/or open AEs, at Investigator discretion on Days 28 through 32

1.3. Schedule of Activities

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

Visit Identifier/Day *[for list of abbreviations refer to **Section 10.10**]*	**Screening ≤-28 to -2**	**Day -1**	**Day 1**												**Day 2**		**Day 3**	**ET**	**Follow-up[a] Day 30±2**
Hours Post Dose		--	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**24**	**36**	**48**	--	--
Informed consent & demography	x																		
Outpatient visit	x																	x	
Inpatient stay at Clinical Research Unit		x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x		
Eligibility assessment	x	x																	
Medical history	x	x																	
Physical exam (height & body weight at screening, only)[b]	x	x															x	x	
Breath alcohol test & Urine drug test	x	x																	
Alcohol/tobacco & contraception use	x	x															x	x	x[c]
(Update) prior/concomitant treatments	x	x																x	x
Single, *supine* 12-lead ECG	x		x														x	x	
Single, *seated* vital signs (BP,pulse rate, temperature)	x	x	x												x		x	x	
Serious and non-serious adverse event monitoring	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x	x
Standard meals[d]		x	x				x			x		x		x	x		x		
Investigational product administration			x[e]																
Blood & Urine for clinical laboratory tests after ≥4-hour fast	x		x														x	x	
Serology for FSH (females only), HbA1c, HIV, HBsAg, HCVAb/RNA	x																		
Serum pregnancy test (females only)	x		x														x	x	
COVID-19 symptoms and risk assessment	x	x																	
COVID-19 testing	x[f]																	x	
Pfizer Prep D1.5 Banked Biospecimen[g]			x																
Blood for pharmacokinetic sampling for PF-06882961			x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	
Blood for unbound fraction protein binding PF-06882961			x				x												
Urine pregnancy test (WOCBP, only)[h]	x	x																	

a. Visit to be performed as telephone contact and must occur 28 to 32 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.

b. Complete physical exam (PE) at screening; at all other time points limited PE , at investigator discretion (see Section 8.2.1).

c. In confirmation of appropriate contraception use only.
d. Meals/snacks to be served at clock times matching approximately 0H, 4H, 7H, 10H, and 14H (optional) relative to dosing on Day 1 (while inpatient).
e. Dosing to occur with standard morning meal provided approximately 30 minutes prior to 0H, and completed approximately 10 minutes prior to dosing.
f. COVID-19 viral test to occur between DAY-5 and DAY-2 to permit availability of test result prior to admission on Day -1.
g. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
h. Test result must be reviewed and deemed acceptable (ie, negative) to continue participation in the study.

2. INTRODUCTION

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

2.1. Study Rationale

The primary purpose of this non-randomized, open-label study is to characterize the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics (PK) of PF-06882961 following administration of a single oral dose of PF-06882961.

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 Overview

2.2.1.1. 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.

CCI

CCI [redacted]

[redacted].

2.2.1.3. Nonclinical Safety

General toxicology studies have been completed in cynomolgus monkeys up to 6 months in duration (with a 3-week lead-in and 1-month recovery) and in rats up to 6 months in duration (with a 1-month recovery). CCI [redacted]

Embryo-fetal developmental studies were completed in rats and rabbits. CCI [redacted]

CCI [redacted]

PF-06882961 was negative in genetic toxicity testing and photosafety endpoints. CCI [redacted]

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

2.2.2. Clinical Overview

Three clinical studies, C3421001, C3421002 and C3421003 have completed dosing with PF-06882961. CCI [redacted] 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 2.2.2.1. Refer to the IB for more details on these studies and the known drug class effects of marketed injectable GLP-1R agonists.

2.2.2.1. Clinical Safety

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

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 1 symptomatic hypoglycemic adverse event (HAE) that was reported in 1 participant in the 120 mg BID group. This AE was non-fasting, mild in severity and of limited duration. No deaths occurred in the C3421002 study. Two 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.

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

2.2.2.2. Clinical Pharmacokinetics

The clinical pharmacokinetics (PK) of PF-06882961 in 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.

CCI [redacted]

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. 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 [redacted]

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-06882961		
Thyroid C-cell tumors	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, dulaglutide, and exenatide) due to dose-dependent and treatment duration-dependent thyroid C-cell tumors in nonclinical studies in rats and mice at clinically relevant exposures. Thyroid C-cell tumors have not been observed with PF-06882961 in clinical or nonclinical studies.	Participants with a personal or family history of medullary thyroid carcinoma or MEN2 are excluded from the clinical development program.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-06882961		
Pancreatitis	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide and dulaglutide). Pancreatitis has not been observed in the PF-06882961 clinical trial program.	The single dose and dose level administered in this study minimize any potential risk.
Hypoglycemia	Clinical trials with injectable GLP-1R agonists have not demonstrated an increased risk for hypoglycemia. However, when administered in combination with anti-diabetic agents that are known to have an increased risk of hypoglycemia (such as insulin or sulfonylureas), an increased risk for hypoglycemia was observed. Only 1 adverse event of mild hypoglycaemia has been reported in the clinical development program to date.	Blood glucose is monitored frequently during clinical studies, and participants are monitored for signs or symptoms of hypoglycemia. The single dose and dose level administered in this study minimize any potential risk.
Impairment in renal function	In rats, minimal renal tubular vacuolation was observed, but this finding was considered to be non-adverse. In the clinical trial program only 1 mild adverse event (PT Blood creatinine increased) has been observed in the clinical trial program.	Study exclusion criteria include participants with significant renal impairment.
Gastrointestinal adverse reactions	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide and dulaglutide). In addition, gastrointestinal adverse events, the majority of which were mild in severity, have been observed in the clinical program with PF-06882961. In nonclinical studies with PF-06882961, gastrointestinal adverse effects have been seen in rats and monkeys.	Participants are monitored during the clinical studies to prevent potential sequelae of any severe gastrointestinal reactions, eg, dehydration. Exclusion criteria include any factor that may affect drug absorption, such as bariatric surgery, active inflammatory bowel disease or any intestinal resection.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-06882961		
Diabetic Retinopathy complications	The potential risk is based on the product labeling for the injectable GLP-1R agonist semaglutide. This risk has not been listed in the prescribing information for other marketed GLP-1R agonists. There are no nonclinical or clinical data involving PF-06882961 to suggest an increased risk of diabetic retinopathy complications.	Potential participants with diabetes mellitus are excluded from this clinical study. In addition, the single dose and dose level administered in this study minimize any potential risk.
Other		
Risk of COVID-19 exposure during study	During the pandemic, study participants could be infected with the SARS-CoV-2 virus during study participation. This could lead to increased health risk for this participant and others in the study.	Participants undergo COVID-19 specific assessments prior to admission to study site and according to SOA.

2.3.2. Benefit Assessment

A single dose of PF-06882961 administered in this study is not expected to provide any clinical benefit to healthy participants or participants with hepatic impairment. This study is designed primarily to characterize the effect of varying degrees of hepatic 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 hepatic impairment.

2.3.3. Overall Benefit/Risk Conclusion

In line with the clinical profile of marketed GLP-1R agonists,[11-13] 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 hepatic impairment.

Considering all available clinical and nonclinical data, the benefit-risk profile of PF-06882961 supports continued clinical development. Based on the safety profile of PF-06882961 observed in clinical studies to date, the risk to the participants in this study is deemed to be minimal. More detailed information about the known and expected benefits

and risks and reasonably expected AEs of PF-06882961 may be found in the IB for PF-06882961, 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 varying degrees of hepatic impairment relative to age- and body weight-matched participants without hepatic impairment.	• Plasma: C_{max}, AUC_{inf}, AUC_{last}, fu as data permit.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of a single oral dose of PF-06882961 when administered to adult participants with varying degrees of hepatic impairment and in age- and body weight-matched participants without hepatic impairment.	• Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To compare additional PK parameters of PF-06882961 following administration of a single oral dose in adult participants with varying degrees of hepatic impairment and in age- and body weight-matched participants without hepatic 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.

4. STUDY DESIGN

4.1. Overall Design

This is a non-randomized, open-label, single-dose, parallel-cohort, multicenter study to investigate the effect of varying degrees of hepatic function on the plasma PK of PF-06882961 after a single, oral 20 mg dose administered in the fed state. A total of approximately 24 participants with varying degrees of hepatic function will be dosed in the study as shown in Table 1.

Table 1. Hepatic Function Categories Based on Child-Pugh Score

Cohort	Description	Child-Pugh Score	Number of Participants
1	Without hepatic impairment	Not Applicable	6[a]
2	Mild hepatic impairment	Class A (5 to 6 points)	6
3	Moderate hepatic impairment	Class B (7 to 9 points)	6
4	Severe hepatic impairment	Class C (10 to 15 points)	6[b]

a. Additional participants may be dosed to a maximum of 8 participants to ensure mean age ±5 years and mean body weight ±10 kg of this cohort is aligned with the pooled average assessed when ≥75% of participants are dosed across the other 3 cohorts.
b. If recruitment across the sites selected proves to be prohibitive, study will dose only 4 participants in this cohort.

Categorization of participants into Cohort 2-4, inclusive, will be done based on Child-Pugh scores determined, as described in Appendix 8 at the screening visit. Participants will be dosed in a staged manner such that those with moderate and severe hepatic impairment (Cohorts 3 and 4) will be evaluated first. Recruitment for participants with mild hepatic impairment (Cohort 2) will initiate when approximately 50% of the total participants in Cohorts 3 and 4 have been dosed. Participants without hepatic impairment (Cohort 1) will be recruited near the end of the study to match the average demographics (at a minimum, age and weight; and gender as much as practically possible) across the pooled Cohorts 2 through 4.

Approval from the Sponsor must be obtained before proceeding with recruitment for participants in Cohort 1 and Cohort 2.

Participants who prematurely discontinue before completing all assessments may be replaced, at the discretion of the principal investigator (PI) and sponsor study team.

The overall study design is summarized in Section 1.2. For individual participants, the total duration of participation from the screening visit to the follow-up visit will range from approximately 5 weeks (minimum) to approximately 9 weeks (maximum).

4.2. Scientific Rationale for Study Design

This study involves participants with varying degrees of hepatic impairment and participants without hepatic impairment, matched for age as well as body weight (and gender as much as practically possible). A single dose of PF-06882961 is proposed, as single dose plasma PK of PF-06882961 is generally predictive of exposure upon repeated dosing and limited accumulation has been observed given the relatively short half-life of the compound.

Following administration of single doses of PF-06882961, the arithmetic mean terminal $t_{½}$ of PF-06882961 ranged from 5-7 hours. Even with a possible modest increase in half-life, serial PK samples will be collected over 48 hours post-dose is expected to adequately characterize the elimination phase of the plasma concentration-time profile in the cohorts with varying degrees of hepatic function.

Based on a review of the effect of hepatic impairment on human pharmacokinetics for compounds cleared in a similar manner to PF-06882961 CCI [redacted] mild hepatic impairment generally results in less than 2-fold increases in plasma exposure.[14] In the same group of compounds, moderate hepatic impairment results in less than 3-fold increases in plasma exposure; however, overall, very limited clinical data are available regarding the effect of severe hepatic impairment CCI [redacted].[15-17]

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, 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%]).

In general, participants with normal hepatic function (Cohort 1) will abstain from concomitant treatments, except for the treatment of adverse events. However use of selected limited prescription and non-prescription medications is permitted (refer to Section 6.5 for details). COVID-19 specific assessments have been incorporated to minimize the risks of COVID-19 related complications to participants and the study site personnel.

Participants with impaired hepatic function (Cohorts 2, 3, and 4) are permitted to be on stable doses of background medications for the management of their concomitant medical condition(s) with some exclusions (Appendix 9).

The Child-Pugh classification (CPC; refer to Appendix 8) will be used to define the 3 cohorts of participants with varying degrees of hepatic impairment. This study will include participants with mild (Child-Pugh Class A, Cohort 2), moderate (Child-Pugh Class B, Cohort 3), and severe (Child-Pugh Class C, Cohort 4) hepatic impairment as well as demographic-matched control participants without hepatic impairment (Cohort 1). All 3 categories of hepatic impairment will be assessed. All participants will be required to provide their own consent to participate in this study, hence participants with clinically-active Grade 3 or Grade 4 encephalopathy will be excluded. However, participants who have a ***previous*** history of Grade 3 or 4 encephalopathy but are currently receiving an intervention [for example: lactulose or lactitol, alone or in combination with rifaximin, and/or neomycin] to manage their encephalopathy-related signs and symptoms are eligible provided the ***on-treatment*** encephalopathy grading at the screening visit is Grade 2 or lower thereby permitting them to provide their own informed consent. Acknowledging the medical state of the population enrolled, certain eligibility criteria for participants with hepatic impairment are distinctly different, with no specific exclusion of participants with Hepatitis B and Hepatitis C in Cohorts 2, 3, or 4.

As stated in Section 2.2.2.2, there appears to be no clear effect of mild renal impairment on PF-06882961 pharmacokinetics. However, to enable a clearer assessment of the effect of hepatic impairment on PF-06882961 disposition, participants will be excluded if there is concomitant clinical evidence of renal impairment, defined as estimated glomerular filtration rate (eGFR) <60 mL/min.

Both women 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.[18]

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

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 hepatic 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. 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 hepatic 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 follow-up visit via telephone contact shown in the schedule of activities during the period of Day 28 to Day 32 (Day 30 ±2).

The end of the study is defined as the date of the follow-up visit via telephone contact, shown in the schedule of activities, for the last participant in the trial globally.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

5.1.1. Participants in All Cohorts

Age and Sex:

1. Male and female participants between the ages of 18 (or the minimum country-specific age of consent if >18) and 70 years, inclusive, at the screening visit:

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

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

Weight:

3. Body mass index (BMI) of 17.5 to 38.0 kg/m^2, inclusive; and a total body weight >50 kg (110 lb), at the screening visit; with a single repeat assessment of total body weight (and hence BMI), ***on a separate day*** permitted to assess eligibility, if needed.

Informed Consent:

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

5.1.2. ***Additional*** Inclusion Criteria for Participants without Hepatic Impairment (Cohort 1 ***Only***)

1. At screening, no clinically relevant abnormalities identified by a detailed medical history, complete physical examination, including blood pressure (BP) and pulse rate measurement, 12-lead ECG and clinical laboratory tests, as assessed by the sponsor-identified central laboratory;

2. At screening, participants must meet the demographic-matching criteria, including:

    - A body weight that is ±10 kg of the average of the pooled hepatic impairment cohorts (Cohorts 2, 3, and 4), as provided by the sponsor;

    - An age that is ±5 years of the average of the pooled hepatic impairment cohorts (Cohorts 2, 3, and 4), as provided by the sponsor;

- ***Attempts will be made*** to ensure that the male-to-female distribution in Cohort 1, is comparable, to that in the pooled hepatic impairment cohorts (Cohorts 2, 3, and 4);

3. No known or suspected hepatic impairment; including at screening, meet **all** the following criteria, as assessed by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed:

   - Alanine aminotransferase (ALT) ≤ upper limit of normal (ULN);
   - Aspartate aminotransferase (AST) ≤ ULN;
   - Total bilirubin ≤ ULN;

     NOTE: Participants with a history of Gilbert syndrome (and hence elevated total bilirubin) are eligible provided direct bilirubin level is ≤ ULN **plus** ALT and AST are ≤ ULN **plus** alkaline phosphatase, hemoglobin, and reticulocyte count are all ≤ ULN;
   - Albumin ≤ ULN;
   - Prothrombin time ≤ ULN.

5.1.3. *Additional* Inclusion Criteria for Participants with Impaired Hepatic Function (Cohorts 2, 3, and 4 *Only*)

1. Stable hepatic impairment that meets the criteria for Class A, B, ***or*** C of the Child-Pugh classification (refer to Appendix 8) with no clinically significant change in disease status within the 28 days prior to the screening visit, as documented by the participant's recent medical history (*for example*: no worsening clinical signs of hepatic impairment, no worsening of total bilirubin or prothrombin time (PT) by more than 50%);

2. Stable concomitant medications for the management of individual participants' medical history; ***on a case-by-case basis***, with input from the sponsor, participants receiving fluctuating concomitant medication/treatment may be considered if the underlying disease is under control;

3. Participant is willing and able to abide by the lifestyle guidelines described in Section 5.3 of this protocol.

5.2. Exclusion Criteria

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

5.2.1. Participants in All Cohorts

Medical Conditions:

1. Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, ileal resection);

   ***NOTE*:** Participants who have undergone cholecystectomy and/or appendectomy are eligible for this study as long as the surgery occurred more than 6 months prior to Screening;

2. At screening, participants with a positive result for human immunodeficiency virus (HIV) antibodies, as assessed by sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed;

3. A diagnosis of type 2 diabetes mellitus (T2DM) that is documented by medical history;

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

Prior/Concomitant Therapy:

6. Use of prior/concomitant therapies as outlined in Section 6.5;

Prior/Concurrent Clinical Study Experience:

7. 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 investigational product used in this study (whichever is longer);

8. Participants with known prior participation (ie, randomized and received at least 1 dose of investigational product) in a study involving PF-06882961;

Diagnostic Assessments:

9. Participants with ANY of the following abnormalities in clinical laboratory tests at Visit 1, as assessed by the study specific laboratory and confirmed by a single repeat test, if deemed necessary:

   - HbA1c ≥6.5%;
   - FPG ≥126 mg/Dl;
   - eGFR<60 mL/min/1.73m^2;

10. A positive urine drug test, for illicit drugs at screening, as assessed by sponsor-identified central laboratory. However, ***participants in Cohorts 2-4, only***, who have been medically prescribed opiates/opioids or benzodiazepines and report the use of these drugs to the investigator at the Screening visit will be allowed to participate;

    ***NOTE*:** repeat urine drug testing is not permitted in this study;

11. At screening ***or*** Day -1, a positive breath alcohol test, as assessed using kits provided by sponsor-identified central laboratory, with a single repeat *on a separate day* permitted to assess eligibility, if needed;

12. A positive COVID-19 test at screening;

Other Exclusions:

13. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing and until the follow-up contact;

14. History of sensitivity to heparin or heparin-induced thrombocytopenia, only if heparin is used to flush intravenous catheters used during serial blood collections;

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

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

5.2.2. ***Additional*** Exclusion Criteria for Participants without Hepatic Impairment (Cohort 1 ***Only***)

Participants presenting with any of the following will not be included in the study:

1. Evidence of chronic liver disease including history of hepatitis, hepatitis B, or hepatitis C or evidence of any of the following, as assessed by sponsor-identified central laboratory, with a single repeat, permitted to assess eligibility, if needed:

   - Hepatitis B virus, defined by presence of hepatitis B surface antigen (HBsAg);

     ***NOTE*:** while *not* part of the tests assessed in this study, participants with a previously positive hepatitis B surface antibody result due to vaccination are deemed eligible;

   - Hepatitis C infection, defined by presence of hepatitis C antibody (HCVAb) ***and*** HCV ribonucleic acid (RNA);

2. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).

3. Screening ***supine*** 12-lead ECG demonstrating QTcF interval >450 msec or a QRS interval >120 msec. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility;

4. Screening ***seated*** systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg, following ≥5 minutes of seated rest. If SBP is ≥140 mm Hg or DBP ≥90 mm Hg, the BP assessment should be repeated 2 more times and the average of the 3 BP values should be used to determine eligibility;

5. Use of ***chronic*** prescription medications within 7 days or 5 half-lives (whichever is longer) prior to Day 1;

   NOTE: Use of selected, limited prescription and non-prescription medications is permitted (refer to Section 6.5 for details);

5.2.3. ***Additional*** Exclusion Criteria for Participants with Impaired Hepatic Function (Cohorts 2, 3, and 4 ***Only***)

Participants presenting with any of the following will ***not*** be included in the study:

1. Hepatic carcinoma ***or*** hepatorenal syndrome ***or*** limited predicted life expectancy (defined as less than 1 year in Cohorts 2 & 3 and less than 6 months for Cohort 4 only);

2. A diagnosis of hepatic dysfunction secondary to any acute ongoing hepatocellular process that is documented by medical history, physical examination, liver biopsy, hepatic ultrasound, computerized tomography scan, or magnetic resonance imaging (MRI);

3. History of surgery that would be expected to alter absorption, distribution, metabolism, or excretion (ADME) properties of PF-06882961 (eg, status post porta-caval shunt surgery);

   NOTE: Participants with a transjugular intrahepatic portosystemic shunt (TIPS) are permitted provided that they meet the Child-Pugh criteria;

4. History of gastrointestinal hemorrhage due to esophageal varices or peptic ulcers less than **4 weeks** prior to Screening;

5. Signs of clinically active Grade 3 or 4 hepatic encephalopathy (ie, >Grade 2 Portal Systemic Encephalopathy score; refer to Appendix 8);

6. Severe ascites and/or pleural effusion, except for those categorized in Cohort 4 who may be enrolled provided participant is medically stable, per the investigators' medical judgment;

7. Participants who have previously received a kidney, liver, or heart transplant;

8. Screening ***supine*** 12-lead ECG demonstrating a QTcF interval >470 msec or a QRS interval >120 msec. If QTcF exceeds 470 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine eligibility;

9. At screening, persistent severe, uncontrolled hypertension; for example: ***seated*** SBP ≥180 mm Hg and/or DBP ≥105 mm Hg after ≥5-minute of seated rest, with a single repeat permitted to assess eligibility, if needed, at each of these 2 visits:

   - For participants with SBP ≥160 (and <179) mm Hg ***or*** DBP ≥100 (and <104) mm Hg, the period between Screening and Day -1 must be used to refine the doses of the agents used for management of BP with the aim to have stable BP by Day 1 [refer to Section 5.2.4];

10. Participants with ALT ***or*** AST >5x ULN on clinical laboratory tests at screening, as assessed by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, if needed.

5.2.4. Criteria for Dosing on Day 1

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

- Breath alcohol test, using kits provided by sponsor-identified central laboratory, on Day -1 is negative;
- In women of childbearing potential, urine pregnancy test on Day -1 is negative as reported by on-site pregnancy test using supplies provided by the sponsor-identified central laboratory;
- Safety-related laboratory tests collected and analyzed by sites' local laboratory on Day -1, ***if performed*** at investigator discretion, upon review on Day 1 must reflect the participant to be in stable medical condition;
- 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 and 3 ***only***: Participants must have measurement on Day 1 of SBP ≤159 mm Hg ***and*** DBP ≤99 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];
- Cohort 4 ***only***: Participants must have measurement on Day 1 of SBP ≤159 mm Hg ***and*** DBP ≤105 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

After confirmation of eligibility, participants will be instructed to maintain the guidelines described below for the duration of participation in the study.

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to all fasting clinical laboratory evaluations and at least 10 hours prior to the collection of the predose PK sample;
- Water may be consumed as desired (ad libitum);

- While inpatient, all meals will be standardized as follows:

  - On Day 1, following an overnight fast of at least 10 hours, participants should begin breakfast approximately 30 minutes prior to PF-06882961 administration. The breakfast will be consumed over approximately a 20-minute period with PF-06882961 administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to complete the entire breakfast. There will be no water restrictions prior to dosing.

  - Standard morning meal, lunch, afternoon snack, and evening meal (and an optional evening snack) will be provided at a similar clock time to the clock time when these meals are provided relative to dosing on Day 1 while inpatient (ie, 0H, 4H, 7H, 10H, and 14H);

  - The total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein. The nutritional macronutrient composition consumed by each participant should be maintained, as much as practically possible;

  - The daily caloric intake per participant should not exceed approximately 3200 kcal;

  - The morning meal (matching 0H), afternoon snack, and optional evening snack is each envisioned to constitute 300 to 400 calories and a macronutrient composition of approximately 55% carbohydrates, 30% fat and 15% protein;

  - Lunch and evening meal ***each*** is envisioned to constitute less than 1000 calories;

  - Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to Day 1 and until collection of the final PK blood sample.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from alcohol for ≥24 hours prior to admission for inpatient stay (plus have a negative breath alcohol test on Day -1) and continue abstaining from alcohol until collection of the final PK blood sample;

- Consumption of caffeinated drinks and tobacco (or nicotine containing products) is permitted during participation in the study; however, there may be a need for brief interruption while at the site, depending on local site policy.

5.3.3. Activity

- Participants will ***not*** be permitted to engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) within 48 hours before each blood sample collection for clinical laboratory tests while participating in the study; physical activity at an individual participant's normal pace is permitted.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (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 dosed on Day 1. Screen failure data are collected and remain as source with only a limited set reported in the clinical database.

In ***this study,*** participants may be re-screened only after contact with Pfizer Clinician. This is permitted when, due to ***logistical constraints***, the maximum period between screening visit and Day 1, of **28 days,** is exceeded. In addition, for participants in Cohorts 2-4, inclusive, ***only***, re-screening may be appropriate following mild intercurrent illness after the condition has resolved. In such cases, all screening procedures must be repeated and the participant assigned a new 8-digit study-specific identification (SSID) number. Participants must be deemed to meet all the eligibility criteria under the new 8-digit SSID *before* progressing to Day 1. Reconsent is required.

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to PF-06882961.

6.1. Study Intervention(s) Administered

PF-06882961 will be supplied by Pfizer as 10 mg tablets in bulk along with individual dosing containers, as necessary, for unit dosing. For the 20 mg dose administered in this study, participants will take 2 tablets of PF-06882961 with the morning meal.

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive breakfast as outlined in Section 5.3.1 (Meals and Dietary Restrictions). The participants will then receive IP at approximately 08:00 hours (plus or minus 2 hours) on Day 1. Investigator site personnel will administer IP with ambient temperature water to a total volume of ***approximately 120 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.

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

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

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

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

6. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

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

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

6.2.1. Preparation and Dispensing

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

Study intervention will be prepared by qualified unblinded site personnel according to the IP manual.

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 Study Intervention

This is an open label, non-randomized study. Following completion of informed consent at the screening visit, each participant will be assigned a single 8-digit SSID number by the site staff. The first 4 digits of the SSID will reflect the sponsor-assigned site number and the remaining 4 digits will reflect each participant's unique number assigned in chronological order of when informed consent is obtained. ***Separately***, prior to dosing on Day 1, each participant will be assigned a 4-digit number consisting of site number (1st digit), cohort (2nd digit) and chronological order of dosing, at a given site (3rd and 4th digit).

6.4. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

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

6.5. Concomitant Therapy

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

Participants with Hepatic Impairment will be allowed to be on certain concomitant medications that have been prescribed. Any concomitant medications may be administered in the morning of Day 1 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 case report form (CRF).

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.

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

Females using hormonal contraceptives or taking hormone replacement therapy are eligible to participate in this study. See Appendix 4 for hormonal contraceptives that are permitted in this study.

6.5.1. Participants without Hepatic Impairment (Cohort 1, Only)

In general, participants in Cohort 1 will abstain from all concomitant treatments, except for the treatment of AEs. Of note, the following ***restrictions:***

- Acetaminophen/paracetamol may be used at doses of ≤1 g/day;
- Herbal supplements must be discontinued ***at least 28 days prior*** to Day 1 and until the follow-up contact;

- Limited use of prescription and nonprescription medications that are not believed to affect the overall results of the study may be permitted on a case by case basis ***after*** approval by the sponsor study team.

6.5.2. Participants with Impaired Hepatic Function (Cohorts 2, 3, and 4)

Participants are permitted to be on stable doses of background medications for the management of their concomitant medical condition(s). ***Whenever possible***, attempts must be made to ***not*** alter the doses and regimens of the concomitant medications after Day 1 and until the follow-up contact.

Participants on certain medications, at the screening visit, are ***excluded*** from the study (see Appendix 9 for details regarding prohibited prior/concomitant medications).

6.5.3. 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.

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

Since this is a single-dose study, this section is not applicable.

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.

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

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow up

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

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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

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

ECGs and vital sign assessments (pulse rate and BP) should be collected prior to any blood draw. If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

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 175 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 issues.

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 limited 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

Blood pressure and pulse rate will be measured as defined in the Schedule of Activities. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

- ***Single, seated*** BP/pulse rate will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mmHg, following a rest of **≥5 minutes**;

- Same arm (preferably the dominant arm) will be used for BP/pulse rate assessment throughout the study;
- BP/pulse rate assessment should not be taken from the arm with an IV catheter, if placed;
- Participants should be instructed not to speak during BP/pulse rate 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

Supine standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc and QTcF intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least **10 minutes** in a supine position.

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 ≥60 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) a postdose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

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

8.2.4. 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. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.5. COVID-19 Specific Assessments

During the screening period, participants will be assessed[19] for COVID-19 related symptoms and risks per local regulations[20] and institutional policies. Participants will also be tested for SARS CoV-2 infection at the timepoints specified in the SoA. Additional testing may be required by local regulations, institutional policies or by the Principal Investigator. The test result must be negative in order for a participant to proceed with admission on Day -1 and dosing on Day 1. COVID-19 tests may be conducted at central or local labs.

8.2.6. Glucose Monitoring

While hypoglycemia is not expected in the study participants, FPG will be measured with laboratory assessments as noted in the SoA. In addition, as a precaution, participants should be monitored for the signs and symptoms associated with hypoglycemia.

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

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

The investigator must assess the glucose values reported by the central laboratory, as well as any signs or symptoms reported by the study participant.

HAE is defined as one of the following:[21]

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

b. 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 at the study site or sponsor identified central laboratory, and the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or IV glucose.

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

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

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

2. The participant exhibited 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 IV glucose.

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

8.2.7. Pregnancy Testing

Pregnancy tests may be urine and/or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until Day 28.

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

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

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly 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 including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

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

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

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

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

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 study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

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

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

Medication errors include:

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

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of PF-06882961 greater than 300 mg within a 24-hour time period ±2 hours will be considered an overdose as this was the highest dose administered in the C3421001 study.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.

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

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

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

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

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

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of PF-06882961

Blood samples of approximately 3 mL, to provide a minimum volume of 1 mL plasma, 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 times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of PF-06882961. Samples collected for analyses of 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. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of study intervention will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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.

8.5.2. Plasma for Determination of PF-06882961 Unbound Fraction Protein Binding

During the study, a blood sample (approximately 12 mL, to provide approximately 5 mL of plasma) to provide sufficient plasma for unbound fraction determination, will be collected into an appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of PF-06882961 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

Samples collected for analyses of PF-06882961 binding 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 study intervention/other will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

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

8.7.2. Banked Biospecimens for Genetics

A 2 mL blood sample optimized for DNA isolation (Prep D1.5) will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

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

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

A sample size of approximately 24 participants (approximately 6 participants per cohort, with varying degrees of hepatic function in each of the 4 cohorts) has been selected to provide sufficient precision to detect a 2-fold difference in AUC_{inf} between each Test cohort (with hepatic impairment) and the Reference cohort (without hepatic impairment). Table 2 presents the 90% CIs (with 80% coverage probability) for various possible effects on AUC_{inf}. The same table would be applicable for possible effects on C_{max}.

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

Estimated Effect (Test/Reference)	AUC_{inf}	
	Probable 90% CI	**Probable CI Width**
75%	43% to 129%	86%
100%	58% to 172%	114%
150%	87% to 259%	172%
200%	116% to 345%	229%
400%	232% to 690%	458%

These estimates are based on an assumed conservative between-participant standard deviation of 0.489 (equivalent to a geometric coefficient of variation of 52%) for $\log_e AUC_{inf}$ (also applicable to $\log_e C_{max}$) based on data from 2 previous studies conducted in healthy volunteers with PF-06882961 administered as a single dose in the fed state (C3421001 & C3421003).

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

9.3. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process.
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.

Participant Analysis Set	Description
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 any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary and selected tertiary/exploratory endpoints.

9.4.1. Pharmacokinetic Analyses

9.4.1.1. Derivation of Pharmacokinetic Parameters

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. The fraction of PF-06882961 unbound in plasma (fu) will be determined and reported for each participant by the analytical lab.

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 plasma concentration.	Observed directly from data.
T_{max}	Time for C_{max}.	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 $AUC_{0\text{-}last}$	$fu*AUC_{last}$.
$AUC_{inf,u}$	Unbound $AUC_{0\text{-}inf}$	$fu*AUC_{inf}$.
$C_{max,u}$	Unbound C_{max}	$fu*C_{max}$.
CL_u/F	Unbound CL/F	$Dose/(AUC_{inf,u})$.
$V_{z,u}$/F	Unbound V_z/F	$Dose/(AUC_{inf,u}*k_{el})$.

* as data permit

9.4.1.2. Statistical Methods for Pharmacokinetic Data

The effect of varying degrees of hepatic impairment on PK parameters will be assessed by constructing 90% CIs around the estimated difference between each of the Test (hepatic impaired) cohorts and the Reference (without hepatic impairment) cohort. A 1-way analysis of variance (ANOVA) will be used to compare the natural log transformed PF-06882961 AUC_{inf}, C_{max}, AUC_{last}, and fraction unbound (fu), as data permit, for each of the hepatic impairment cohorts (Test) to the cohort without hepatic impairment (Reference). Estimates of the adjusted mean differences (Test - Reference), and corresponding 90% confidence intervals, will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

Additional exploratory analysis using linear regression will be used to analyze the potential relationship between appropriate PK parameters [eg, AUC_{inf}, AUC_{last}, C_{max} and fu] and hepatic function (eg, serum albumin concentration, prothrombin time or total bilirubin). Plots of PK parameters (eg, AUC_{inf}, AUC_{last}, C_{max} and fu) versus hepatic function will be constructed, with a regression line and 90% confidence region included. Estimates of the slope and intercept, together with a 90% CI, and the coefficient of determination (ie, R-squared and adj-R-squared) will be obtained from the model.

Additionally, as an exploratory analysis, age and body weight may be explored as an additional covariate/factor in the models, as appropriate.

Individual PF-06882961 concentrations will be listed and summarized descriptively by nominal PK sampling time and hepatic function cohort. Individual participant and summary profiles of the concentration-time data will be plotted by hepatic function cohort for both total plasma PF-06882961 and unbound PF-06882961.

PF-06882961 $AUC_{inf,}$ AUC_{last}, C_{max}, unbound AUC_{inf} ($AUC_{inf,u}$), unbound AUC_{last} ($AUC_{last,u}$), and unbound C_{max} ($C_{max,u}$) individual participant parameters will be plotted by hepatic function cohort. PK parameters of PF-06882961 will be summarized descriptively by hepatic function cohort. Unbound fraction (fu) will be listed and summarized descriptively by hepatic function cohort.

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 hepatic function cohort.

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

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 Analyse(s)

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

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. 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 modeling, and/or supporting clinical development.

9.6. Data Monitoring Committee or Other Independent Oversight 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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

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

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the SMP.

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

10.1.8. Study and Site Start and Closure

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

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

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

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

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

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

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

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

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

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

10.2. Appendix 2: Clinical Laboratory Tests

The following 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 issues.

Table 4. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Reticulocyte count (Abs) MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine eGFR eGFR) Glucose (fasting) Calcium Sodium Potassium Chloride Phosphorus Total CO_2 (Bicarbonate) AST ALT Alkaline phosphatase GGT Total bilirubin Direct bilirubin[a,b] Indirect bilirubin[a,b] Creatine kinase[a,c] Uric acid Albumin Total protein Amylase Lipase	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[d]	Other tests as part of clinical laboratory tests: • aPTT, PT, PT control, INR • Serum FSH[e] • Serum[f] and urine[g] pregnancy test • Breath alcohol test[g] • Urine drug test[h] • Serology[i]: HBsAg, HCVAb (and if positive, reflex HCV RNA), and HIV • HbA1c • COVID-19 test[j]
Additional Tests (Needed for Hy's law)			
AST ALT Total bilirubin Albumin Alkaline phosphatase Direct bilirubin	Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug levels and/or protein adduct level		

a. At screening and Day 1, ***only***.
b. After Day 1, direct and indirect bilirubin assessed when total bilirubin is > ULN***, only***.
c. After Day 1, creatine kinase assessed when ALT is > ULN, ***only***.
d. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
e. To be assessed in ***all*** females (at screening ***only***).
f. Serum testing in ***all*** females at all times when safety-related laboratory assessments are performed; urine testing to be done on-site using kits provided by sponsor-identified central laboratory, in WOCBP, only.
g. Testing to be performed on-site, at screening and Day -1, only using kits provided by sponsor-identified central laboratory.
h. For urine drug test, minimum requirements include cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.
i. At screening, ***only***.
j. May be conducted at central or local laboratory.

For list of abbreviations, refer to Section 10.10.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

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

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

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

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

10.3.2. Definition of SAE

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

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

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording/Reporting

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

occupational exposure.

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

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

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

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

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

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. 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.

3. Postmenopausal female.

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a

     - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

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

10.4.4. Contraception Methods

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

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential 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.

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

    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation.

    - Oral;
    - Injectable.

8. Sexual abstinence.

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

In addition, 1 of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

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

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

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

- The samples will be retained as indicated:

    - Samples for banking will be stored indefinitely or for another period as per local requirements.

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

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

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

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

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

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

ECG Findings That Qualify as SAEs

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

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

10.8. Appendix 8: Child-Pugh Classification (CPC) of Liver Dysfunction

Table 5. Scoring for Child Pugh Classification[22]

Cohort	CPC	Level of dysfunction	Total Score (tally based on assessment of parameters in Table 6)
1	Not Applicable	Without hepatic impairment	Not Applicable
2	A	Mild	5-6
3	B	Moderate	7-9
4	C	Severe	≥10

Table 6. Derivation of Child Pugh Classification Score

Assessment Parameters	Assigned score for observed findings		
	1 point	2 points	3 points
Encephalopathy grade[a] (refer to Table 7 below)	0	1 or 2	3 or 4[a]
Ascites	Absent	Asymptomatic	Requiring intervention
Serum total bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, sec prolonged	<4	4 to 6	>6

a. Participants with a prior history of Grade 3 or 4 encephalopathy who are *currently* receiving an intervention [*for example*: lactulose or lactitol, alone or in combination with rifaximin, and/or neomycin] to manage encephalopathy-related signs and symptoms should be scored for encephalopathy grading *based on their presentation while on intervention at the screening visit* and can be included in Study C3421014 so long as they do ***not*** have clinically active Grade 3 or 4 encephalopathy.

Table 7. Determination of Encephalopathy Grade

Encephalopathy Grade	Definition
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia
3[a]	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity
4[a]	Unrousable coma, no personality/behavior, decerebrate

a. Subjects with clinically active Grade 3 or 4 encephalopathy are excluded.

CPC should be assessed at screening, *only* to determine the classification of a given participant.

10.9. Appendix 9: Prohibited Prior/Concomitant Medications

The following medications are prohibited until the follow-up visit (ie, 28-32 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).	Day -1 to 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

10.10. Appendix 10.Abbreviations

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

	Term
Abs	Absolute
ADME	absorption, distribution, metabolism, or excretion
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{24}	area under the plasma concentration-time profile from time zero to the time 24 hours
AUC_{24}, free	unbound Area under the plasma concentration-time profile from time zero to the 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
$AUC_{0\text{-}inf}$	The total AUC or $AUC_{0\text{-}\infty}$ is the area under the curve 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
$AUC_{last,u}$	unbound area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
$AUC_{0\text{-}last}$	Area under the plasma concentration-time profile from time zero to the last measured concentration ($AUC_{0\text{-}last}$)
$AUC_{24,}$ total	Total Area under the plasma concentration-time profile from time zero to the time 24 hours
AV	atrioventricular
BCRP	breast cancer resistance protein
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C	Celsius
cAMP	cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	apparent clearance of drug from plasma

	Term
CLu/F	unbound apparent clearance from plasma
C_{last}	last quantifiable concentration
C_{max}	maximum observed concentration
$C_{max,}$ free	unbound maximum plasma contentration
$C_{max,}$ total	total maximum plasma concentration
$C_{max,u}$	unbound maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease
CPC	Child-Pugh classification
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTMS	clinical trial management system
Cu	cubic
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DPP	dipeptidyl peptidase 4
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EFD	Embryo fetal developmental
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ET	Early Termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
Fu	fraction unbound
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
HAE	Hypoglycemic adverse event

	Term
HbA1c	Glycated hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	Heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
INR	international normalized ratio
IP	investigational product
IPAL	investigational product administration log
IR	Immediate release
IRB	Institutional Review Board
IV	intravenous
IVGTT	intravenous glucose tolerance test
K2EDTA	dipotassium ethylenediaminetetraacetic acid
K_{el}	terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
LFT	liver function test
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MEN2	multiple endocrine neoplasia syndrome type 2
MRI	magnetic resonance imaging
Msec	millisecond(s)
MTC	medullary thyroid carcinoma
N/A	not applicable
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OCT2	organic cation transporter 2
OATP	organic anion-transporting polypeptide
PD	pharmacodynamic(s)
PE	Physical exam
PI	principal investigator
PK	pharmacokinetic(s)
PR	pulse rate
PT	prothrombin time

	Term
PVC	premature ventricular contraction
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
Qual	qualitative
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SMP	study monitoring plan
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SSID	study-specific subject identification
SToD	study team on demand
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal phase half-life
T2DM	type 2 diabetes mellitus
TBili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TIPS	transjugular intrahepatic portosystemic shunt
T_{max}	time to reach C_{max}
UGT	uridine 5'-diphosphate-glucuronosyltransferase
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution
$V_{z,u}/F$	unbound apparent volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential

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