A PHASE 1, OPEN -LABEL, FIXED SEQUENCE STUDY TO EVALUATE THE EFFECT OF TWO STEADY STATE DOSE LEVELS OF PF-06882961 ON THE PHARMACOKINETICS OF SINGLE ORAL DOSES OF ROSUVASTATIN AND MIDAZOLAM IN OTHERWISE HEALTHY ADULT PARTICIPANTS WITH OBESITY

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Short Title: A Phase 1 Study To Evaluate The Effect Of Two Steady State Doses of PF-06882961 On Rosuvastatin And Midazolam Pharmacokinetics In Otherwise Healthy Adult Participants With Obesity.

Protocol Amendment Summary of Changes Table

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1. PROTOCOL SUMMARY

1.1. Synopsis

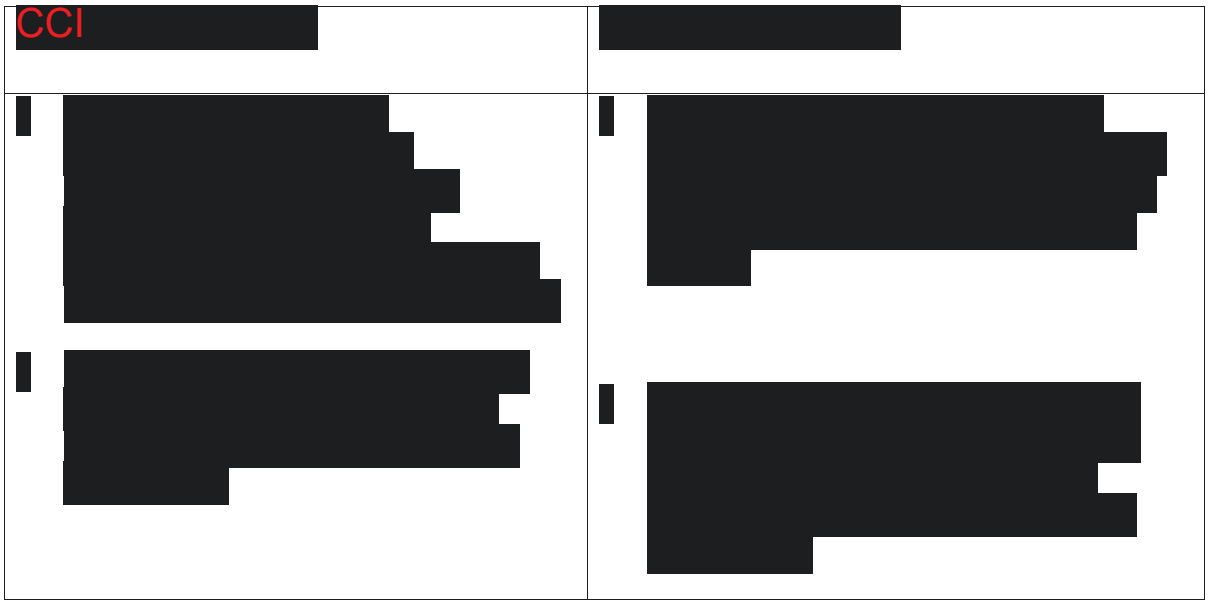
Short Title: A Phase 1 Study To Evaluate The Effect Of Two Steady State Doses of PF-06882961 On Rosuvastatin And Midazolam Pharmacokinetics In Otherwise Healthy Adult Participants With Obesity.

Rationale

This is a Phase 1, open-label study to evaluate the effect of two steady state dose levels of PF-06882961 on the pharmacokinetics of rosuvastatin and midazolam in otherwise healthy, adult participants with obesity. This study is intended to generate safety, tolerability, and pharmacokinetic data for further clinical development.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the effects of PF-06882961 on the pharmacokinetics of rosuvastatin in otherwise healthy adult participants with obesity. • To evaluate the effects of PF-06882961 on the pharmacokinetics of midazolam in otherwise healthy adult participants with obesity.	• Rosuvastatin plasma pharmacokinetic parameters: AUC_{inf} (if data permits* otherwise AUC_{last}) in Periods 1, 4 and 7. • Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permits* otherwise AUC_{last}) in Periods 2, 5 and 8.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-06882961 administered separately and in combination with rosuvastatin or midazolam, in otherwise healthy adult participants with obesity.	• Assessment of treatment-emergent adverse events, clinical laboratory abnormalties, vital signs, body weight, and ECG parameters during the entire study. • Assessment of mental health as determined by C-SSRS and PHQ-9 during the entire study.



* Should it be deemed that too few AUC_{inf} estimates (eg, less than 12 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary endpoint for CSR reporting. This will be considered for the rosuvastatin and midazolam objectives separately.

Overall Design

This study is a Phase 1, open-label, 8-period, fixed-sequence study to evaluate the effect of PF-06882961, administered at two steady-state dose levels, on the pharmacokinetics of rosuvastatin and midazolam, administered separately as single doses, in otherwise healthy adult participants with obesity. The total duration of participation from the Screening Visit to the FU contact will be approximately 17 weeks.

Number of Participants

A sample size of approximately 16 participants will be enrolled such that approximately 12 evaluable participants complete the study. This minimum number of evaluable participants has been selected to provide sufficient precision to detect a 1.25-fold difference in AUC_{inf} for either rosuvastatin or midazolam.

Intervention Groups and Duration

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

The purpose of this study is to characterize the effect of PF-06882961, administered at two steady-state dose levels, on the PK of single doses of rosuvastatin (10 mg) and midazolam (2 mg), administered separately, in adult participants with obesity. A multiple dose study will be conducted to ensure maximal clinically relevant steady-state PF-06882961 exposures are achieved. The drug-drug interaction effect will be initially assessed at PF-06882961 120 mg BID CCI

CCI [redacted] and again at 200 mg BID CCI [redacted]

PF-06882961 will be provided as tablets for oral administration. Study intervention (PF-06882961) must be administered BID within approximately 10 minutes of completion of the morning and evening meals, approximately 10 hours apart. Rosuvastatin and midazolam will be administered within approximately 10 minutes of completion of the morning meal. PF-06882961 will be administered first and midazolam/rosuvastatin will be administered within 5 minutes of PF-06882961.

The total duration of participation from the Screening Visit to the FU contact will be approximately 17 weeks ie, 117 days, of which up to 63 days will be inhouse (Period 1 (rosuvastatin): 5 days, Period 2 (midazolam): 2 days, Period 3 (PF-06882961): 29 days, Period 4 (PF-06882961+rosuvastatin): 4 days, Period 5 (PF-06882961 + midazolam): 1 day, Period 6 (PF-06882961): 16 days, Period 7 (PF-06882961+rosuvastatin): 4 days, Period 8 (PF-06882961 + midazolam): 2 days, FU visit 7-10 days from last dose study intervention and FU contact 28-35 days from last dose study intervention).

Participants may be discharged on Period 2, Day 2 and return to the CRU for Period 3, Day-1 within 7 days from discharge. Alternatively, participants may remain as inpatient on Period 2, Day 2 and begin Period 3, Day 1 activities the same day, without completing Period 3, Day -1 procedures.

Data Monitoring Committee or Other Independent Oversight Committee: No

This study will not use a DMC.

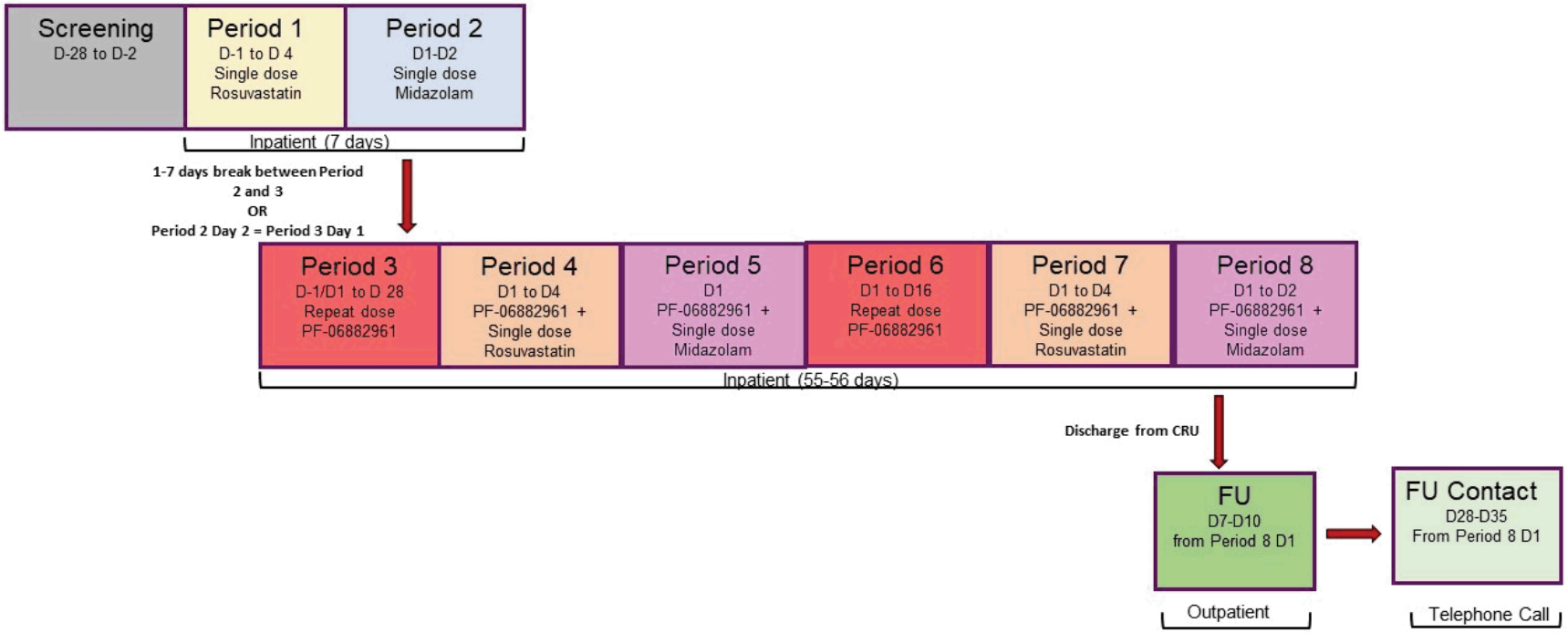
Statistical Methods

The PK data for CCI [redacted] rosuvastatin and midazolam will be analyzed and reported separately.

Natural log-transformed AUC_{inf} (as data permit) of rosuvastatin administered alone or co-administered with PF-06882961 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-reference) and corresponding 90% confidence intervals will be obtained from the models. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. The two test treatments will be 'rosuvastatin and PF-06882961 120 mg BID' (Period 4) and 'rosuvastatin and PF-06882961 200 mg BID' (Period 7), which will be reported separately in comparison to the reference treatment of 'rosuvastatin alone' (Period 1). The same analysis for CCI [redacted] AUC_{last} of rosuvastatin will also be conducted.

Natural $\log_e$-transformed AUC_{inf} (as data permit)[redacted] and AUC_{last} of midazolam administered alone or co-administered with PF-06882961 will be analyzed and reported separately using the same mixed effect model as described above for rosuvastatin. The two test treatments will be 'midazolam and PF-06882961 120 mg BID' (Period 5) and 'midazolam and PF-06882961 200 mg BID' (Period 8), which will be reported separately in comparison to the reference treatment of 'midazolam alone' (Period 2).

1.2. Schema



Follow-Up (FU) visit 7-10 days from last dose of study intervention. A FU Contact visit will be 28-35 days after last dose of study intervention.

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.

Table 1. Overall Schedule of Activities through Period 5

Visit Identifier	Screening	Period 1 (Rosuvastatin only)					Period 2 (Midazolam only)		Period 3 (PF-06882961 only)										Period 4 (PF-06882961 + rosuvastatin)				Period 5 (PF-06882961 + midazolam)
Day in Study Period[a]	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**1**	**2**	**-1**[c]	**1**	**2-7**	**8**	**9-14**	**15**	**16-21**	**22**	**23-27**	**28**	**1**	**2**	**3**	**4**	**1**
Days in Study[b]	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**[c]	**8**	**9-14**	**15**	**16-21**	**22**	**23-28**	**29**	**30-34**	**35**	**36**	**37**	**38**	**39**	**40**
Informed consent & demography	x																						
Outpatient visit (after ≥10-h fast)	x																						
COVID-19 pre-screening[d]	x	x							x[e]														
COVID-19 testing[d]	x	x				x			x[e]		x[e]												
Temperature check[d]	x	x	→	→	→	→	→	x[e]/→	x[e]	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Inpatient stay at CRU		x	→	→	→	→	→	x[e]/→	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Eligibility Criteria	x	x																					
Medical history	x																						
C-SSRS and PHQ-9	x	x								x		x		x		x			x				
Review drug, alcohol/tobacco use	x	x							x														
Review contraception use (Section 5.3.4)	x	x							x														
Review prior or concomitant treatments	x	x	→	→	→	→	→	x/→	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse event monitoring	x	x	→	→	→	→	→	x/→	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Standardized meals/snacks[e]		x	→	→	→	→	→	x/→	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Physical exam[f] (height at Screen only)	x								x														
Body weight	x		Table 3				Table 4			x		x		x		x		Table 5	Table 3				Table 4
Supine 12-lead ECG	x									x		x		x		x							
Single, supine vital signs assessment[g]	x									x		x		x		x							
PF-06882961 administration[h]										x	x	x	x	x	x	x	x			x	x	x	
Rosuvastatin administration																							
Midazolam administration																							
Blood Sampling for:[i]																							
-Chemistry	x									x		x		x		x							
- Hematology	x									x													
- PT/INR/aPTT	x									x										**x**			
- FSH[j], HIV, HepBsAg, HCVAb, HCV RNA, C-peptide	x																						
- HbA1c, TSH, lipids	x									x										x			

Table 1. Overall Schedule of Activities through Period 5

Visit Identifier	Screening	Period 1 (Rosuvastatin only)					Period 2 (Midazolam only)		Period 3 (PF-06882961 only)										Period 4 (PF-06882961 + rosuvastatin)				Period 5 (PF-06882961 + midazolam)
Day in Study Period[a]	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**1**	**2**	**-1[c]**	**1**	**2-7**	**8**	**9-14**	**15**	**16-21**	**22**	**23-27**	**28**	**1**	**2**	**3**	**4**	**1**
Days in Study[b]	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7[c]**	**8**	**9-14**	**15**	**16-21**	**22**	**23-28**	**29**	**30-34**	**35**	**36**	**37**	**38**	**39**	**40**
- Free T4, calcitonin, amylase, lipase, total bile acids	x									x										x			
- Serum pregnancy test[j]	x	x							x[j]														
- Rosuvastatin PK				x[k]	x[k]	x[k]														x[k]	x[k]	x[k]	
- Midazolam PK								x[l]															
CCI [redacted]																							
[redacted]																							
[redacted]																							
Urine Sampling for:																							
- Urine drug test[o]	x	x							x														
- Urinalysis (and microscopy, as appropriate)	x									x				x									

a. Day relative to start of dosing Day 1 of that Period.

b. Day relative to first dose of rosuvastatin on Day 1 of Period 1.

c. Discharge from CRU. Participants may be discharged on Period 2, Day 2 and return to the CRU for Period 3, Day-1 within 7 days from discharge. Alternatively, participants may remain as inpatient on Period 2, Day 2 and begin Period 3, Day 1 activities the same day, without completing Period 3, Day -1 procedures. Temperature check, COVID-19 pre-screening, and COVID-19 testing to be performed ***only*** if participant was discharged between Period 2, Day 2 and returns to CRU for Period 3, Day -1.

d. COVID-19 test must be negative prior to admission (Period 1, Day 1 and Period 3 Day -1). Participants will be tested for SARS-COVID-19 infection by PCR. A subsequent test will be done after 4 days ie, completion of 4 x 24 hours in house, or if they develop COVID-19 like symptoms). Prior to COVID-19 test, temperature check and COVID-19 pre-screening (check exposure to positive subject, residence or travel in area of high incidence and COVID-19 related signs and symptoms) will be done.

e. Meals to be provided at approximately 0H, 4H, and 10H post AM dose; plus, snacks provided according to Section 5.3.1.

f. Complete physical exam at Screening and only on Period 3 Day -1 if discharged after Period 2; otherwise, brief exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.

g. Includes blood pressure and pulse rate predose.

h. Dosing to occur BID with breakfast and dinner Section 5.3.1.

i. Collection following fasting duration specified in Section 5.3.1.

j. Testing in females only : Serum β-hCG for all WOCBP; FSH for female participants to confirm post-menopausal status only. Serum pregnancy test should be performed if participant is re-admitted on Day-1 of Period 3. Test result should confirm no pregnancy prior to dosing.

k. For Periods 1 and 4, rosuvastatin PK should be obtained at 24H, 48H, 72H post rosuvastatin dose on Day 1 of the same periods and 96H (ie, Period 2 Day 1 and Period 5 Day 1 predose).

l. For Periods 2 and 5, midazolam PK should be obtained at approximately 24H post midazolam dose on Day 1 of the same periods (ie, Period 2 Day 2 and Period 6 Day 1 predose).

CCI [redacted]

o. Participants may undergo random urine drug testing at the discretion of the investigator.

Table 2. Overall Schedule of Activities Period 6 to ET

Visit Identifier	Period 6 (PF-06882961 only)					Period 7 (PF-06882961 + rosuvastatin)				Period 8 (PF-06882961 + midazolam)		FU	FU Contact Telephone	ET
Day in Study Period[a]	**1**	**2-8**	**9**	**10-15**	**16**	**1**	**2**	**3**	**4**	**1**	**2**	**-**	**-**	**-**
Days in Study[b]	**41**	**42-48**	**49**	**50-55**	**56**	**57**	**58**	**59**	**60**	**61**	**62**	**68-71**	**89-96**	**-**
Informed consent & demography														
Outpatient visit (after ≥10-h fast)												x		
COVID-19 pre-screening														
COVID-19 testing										x				x
Temperature check	→	→	→	→	→	→	→	→	→	→	x			
Inpatient stay at Clinical Research Unit	→	→	→	→	→	→	→	→	→	→	x[c]			
Eligibility Criteria														
Medical history														
CSSR-S and PHQ-9	x		x		x						x	x		x
Review drug, alcohol/tobacco use												x		
Review contraception use (Section 5.3.4)												x	x	x
Review prior or concomitant treatments	→	→	→	→	Table 5	Table 3	→	→	→	Table 4	x	x	x	x
Adverse event monitoring	→	→	→	→			→	→	→		x	x	x	x
Standardized meals/snacks[d]	→	→	→	→			→	→	→		x			
Physical exam (height at Screen only)											x[e]	x[e]		x[e]
Body weight	x		x								x	x		x
Supine 12-lead ECG	x		x									x		x
Single, supine vital signs assessment[f]	x		x									x		x
PF-06882961 administration[g]	x	x	x	x			x	x	x					
Rosuvastatin administration														
Midazolam administration														
Blood Sampling for[h]**:**														
- Chemistry	x		x								x	x		x
- Hematology											x	x		x
- PT/INR/aPTT											x	x		x
- FSH[i] HIV, HepBsAg, HCVAb, C-peptide														
- HbA1c, TSH, lipids											x	x		x
- Free T4, calcitonin, amylase, lipase, total bile acids											x	x		x

Table 2. Overall Schedule of Activities Period 6 to ET

Visit Identifier	Period 6 (PF-06882961 only)					Period 7 (PF-06882961 + rosuvastatin)				Period 8 (PF-06882961 + midazolam)		FU	FU Contact Telephone	ET
Day in Study Period[a]	**1**	**2-8**	**9**	**10-15**	**16**	**1**	**2**	**3**	**4**	**1**	**2**	**-**	**-**	**-**
Days in Study[b]	**41**	**42-48**	**49**	**50-55**	**56**	**57**	**58**	**59**	**60**	**61**	**62**	**68-71**	**89-96**	**-**
- Serum pregnancy test[i]												x		x
- Rosuvastatin PK							x[j]	x[j]	x[j]					x
- Midazolam PK	x[k]										x[k]			x
CCI														
														C
Urine Sampling for:														
- Urine drug test[m]														
- Urinalysis (and microscopy, as appropriate)	**x**										**x**	**x**		x

a. Day relative to start of dosing Day 1 of that Period.

b. Day relative to first dose of investigational product (rosuvastatin) on Day 1.

c. Discharge from CRU.

d. Meals to be provided at approximately 0H, 4H, and 10H post AM dose; plus, snacks provided according to Section 5.3.1. Note that there is no PF-06882961 administration on Day 62.

e. Complete physical exam at Period 8 Day 2 and FU; otherwise, brief exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.

f. Includes blood pressure and pulse rate predose.

g. Dosing to occur BID with breakfast and dinner. Note that there is no PF-06882961 administration on Day 62.

h. Collection following fasting duration specified in Section 5.3.1.

i. Testing in females only: Serum β-hCG for all WOCBP; FSH for female participants to confirm post-menopausal status only.

j. In Period 7, rosuvastatin PK should be obtained at 24H, 48H, 72H, 96H (ie, Period 8 Day 1) post rosuvastatin dose on Day 1 of the same period.

k. In Period 8, midazolam PK should be obtained at approximately 24H post midazolam dose on Day 1 of the same period.

C
C
.

m. Participants may undergo random urine drug testing at the discretion of the investigator.

Table 3. Schedule of Activities –Day 1 of Period 1 (Rosuvastatin ONLY), Period 4 (Rosuvastatin + PF-06882961), and Period 7 (Rosuvastatin + PF-06882961)

Hours Relative to Dosing at 0H	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**16**
Body Weight	x										
Supine 12-lead ECG	x										
Supine vital sign assessment[a]	x										
Rosuvastatin administration	x										
PF-06882961 administration ***(Periods 4 and 7 only)***	x[b]								x[c]		
Blood sampling for:[d]											
- Chemistry	x										
- Hematology ***(Periods 1 and 4 only)***	x										
- CCI [redacted]	[redacted]										
[redacted]	[redacted]										
- Rosuvastatin PK	x	x	x	x	x	x	x	x	x	x	x
CCI [redacted]	[redacted]										
Urine sampling for:											
- Urinalysis and microscopy, as appropriate (***Period 1 only***)	x										

a. Includes blood pressure and pulse rate.

b. Dosing expected to occur with breakfast.

c. Dosing expected to occur with dinner.

d. Collection following fasting duration according to dosing frequency as specified in Meals and Dietary Restrictions.

C [redacted]

f. For Periods 4 and 7 only, PF-06882961 PK sample to be drawn at 0H, approximately 24H after PF-06882961 morning dose on previous day.

Table 4. Schedule of Activities –Day 1 of Period 2 (Midazolam ONLY), Period 5 (Midazolam + PF-06882961) and Period 8 (Midazolam + PF-06882961)

Hours Relative to Dosing at 0H	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**
Supine 12-lead ECG	x										
Supine vital sign assessment[a]	x										
Midazolam administration	x										
PF-06882961 administration ***(Periods 5 and 8 only)***	x[b]								x[c]		
Blood sampling for:[d]											
- Rosuvastatin PK	x										
- Midazolam PK	x	x	x	x	x	x	x	x	X	x	x
- CCI	[redacted]										

a. Includes blood pressure and pulse rate.

b. Dosing expected to occur with breakfast.

c. Dosing expected to occur with dinner.

d. Collection following fasting duration according to dosing frequency as specified in Meals and Dietary Restrictions.

Table 5. Schedule of Activities –Day 28 of Period 3 and Day 16 of Period 6 (PF-06882961 only)

Hours Relative to Dosing at 0H	0	1	2	4	6	8	10	12	14
Supine 12-lead ECG	x								
Supine vital sign assessment[a]	x								
PF-06882961 administration	x[b]						x[c]		
Blood sampling for:[d]									
CCI									
Urine sampling for:									
- Urinalysis and microscopy, as appropriate	x								

a. Includes blood pressure and pulse rate.

b. Dosing expected to occur with breakfast.

c. Dosing expected to occur with dinner.

d. Collection following fasting duration according to dosing frequency as specified in Meals and Dietary Restrictions.

2. INTRODUCTION

PF-06882961 is an oral glucagon-like peptide 1 receptor (GLP-1R) agonist that is currently being developed for the treatment of type 2 diabetes mellitus.

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 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. PF-06882961 is currently being investigated as an adjunct to diet and exercise to improve glycemic control in adult participants with T2DM.

2.1. Study Rationale

The purpose of this phase 1, open-label, eight-period, fixed-sequence study is to evaluate the effect of two dose levels of PF-06882961 administered at steady state on the pharmacokinetics of rosuvastatin and midazolam, administered separately, in otherwise heathy adult participants with obesity.

2.2. Background

T2DM is estimated to affect more than 424 million people worldwide,[5] and the prevalence of T2DM within the United States (US) is estimated to range from 12 to 14%.[6] 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.[7] 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 more than one marketed agent demonstrating cardiovascular benefit.[8] Based on the clinical history of injectable GLP-1R agonists, an oral, small molecule GLP-1R agonist is expected to improve glucose control and reduce HbA1c levels in patients with T2DM, while decreasing appetite and body weight and avoiding the subcutaneous injection required by currently available peptidic GLP-1R agonists.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

2.2.3. Nonclinical Safety

General toxicology studies have been completed in cynomolgus monkeys up to 6 months in duration (with a 3-week lead-in and 1-month recovery) and in rats up to 6 months in duration with a 1-month recovery. The exposure limits for plasma concentrations of PF-06882961 for clinical studies are based on the exposure at the NOAEL dose of 250 mg/kg/day in the 6-month with 1-month recovery toxicology study in rats, due to the fact that findings in monkeys such as decreased food intake and body weight loss are reversible and monitorable in a clinical setting. In the 6-month toxicity study in rats with 1-month recovery the NOAEL was 250 mg/kg/day based on species specific toxicity at a higher dose. CCI [redacted]

CCI [redacted]

CCI [redacted]

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

CCI [redacted]

In embryo fetal studies conducted in rabbits, the NOAEL for maternal and developmental toxicity was 250 mg/kg/da CCI [redacted]

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

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

2.2.4. Clinical Overview

As of the protocol finalization date, 3 clinical studies, C3421001, C3421002 and C3421003 have completed dosing with PF-06882961. In C3421001 and C3421003, single oral doses of PF-06882961 up to 300 mg (or matching placebo) were generally safe and well-tolerated in healthy adult participants. In the multiple dose study C3421002, PF-06882961 doses up to 120 mg BID (or matching placebo) for 28 days were generally safe and well-tolerated in adult participants with T2DM on a background of metformin therapy, and safety results from this study are provided in Section 2.2.4.1. Refer to the IB for more details on these studies and the known drug class effects of marketed injectable GLP1R agonists.

2.2.4.1. Clinical Safety

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

In study C3421002, PF-06882961 doses ranging from 10 mg BID to 120 mg BID were generally safe and well tolerated. A total of 98 participants with T2DM on a background of metformin were randomized to receive PF-06882961 or matching placebo in a 3:1 randomization ratio, and 92 participants completed the study. Six participants discontinued from the study, of which 2 discontinuations were due to treatment-related treatment emergent adverse events (TEAEs), and 4 withdrew during the treatment or follow-up period for non-treatment related reasons.

A total of 319 TEAEs were reported, of which the majority of the AEs (294 or 92%) were mild in intensity, 23 (or 7%) were moderate, and 2 (or 1%) were severe in intensity. The most frequently reported TEAEs were nausea (49.0%), dyspepsia (32.7%), vomiting (26.5%), diarrhea (24.5%), headache (23.5%), and constipation (20.4%). One participant experienced a TEAE of hypoglycemia, which 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 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,[8,9] 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.

2.2.4.2. Clinical Pharmacokinetics

CCI [redacted]

In study C3421002, following 28 days of dosing to participants with T2DM, accumulation was modest for the BID IR formulation treatments CCI [redacted] 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. CCI [redacted]

In study C3421003, 12 healthy participants were randomized to receive single doses of different oral formulations of PF-06882961.

2.3. Benefit/Risk Assessment

PF-06882961 is not expected to provide any clinical benefit to otherwise healthy participants with obesity in this study. This study is designed primarily to generate safety, tolerability, and pharmacokinetic data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06882961 may be found in the investigator's brochure, which is the SRSD for this study. The SRSD for the site sourced rosuvastatin (eg, Crestor) agent is the United States package insert (USPI).[10] The SRSD for the site sourced midazolam (eg, Nayzilam) agent is the United States package insert (USPI).[11]

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention PF-06882961		
Thyroid C-cell tumors	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, dulaglutide, and exenatide) due to dose-dependent and treatment duration-dependent thyroid C-cell tumors in nonclinical studies in rats and mice at clinically relevant exposures. Thyroid C-cell tumors have not been observed with PF-06882961 in clinical or nonclinical studies.	Potential participants with a personal or family history of medullary thyroid carcinoma or MEN2 are excluded from the clinical development program. Thyroid function tests are included in the clinical trial protocols to monitor participants' thyroid function.
Pancreatitis	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide and dulaglutide). Pancreatitis has not been observed in the PF-06882961 clinical trial program.	Per exclusion criteria, potential participants with acute pancreatitis or a history of chronic pancreatitis are not eligible for study entry. Serum amylase and lipase are monitored during the clinical studies.
Hypoglycemia	Clinical trials with injectable GLP-1R agonists have not demonstrated an increased risk for hypoglycemia. However, when administered in combination with anti-diabetic agents that are known to have an increased risk of hypoglycemia (such as insulin or sulfonylureas), an increased risk for hypoglycemia was observed. Participants with obesity who do not have co-existing type 2 diabetes mellitus would not be taking anti-diabetic agents and therefore would not be expected to have an increased risk for hypoglycemia. Only one adverse event of mild hypoglycemia has been reported in the clinical development program to date.	Anti-diabetic medications are prohibited in this study, and blood glucose is monitored as a part of the lab assessments at every clinical visit in this study. Participants are informed about the signs and symptoms of hypoglycemia, and are monitored for these symptoms during the study.

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 one mild adverse event (Preferred Term Blood creatinine increased) has been observed in the clinical trial program.	Per exclusion criteria, potential participants with significant renal impairment are not eligible for study entry. Renal function is monitored at frequent intervals by lab assessments of serum blood urea nitrogen (BUN), creatinine and Estimated Glomerular Filtration Rate (eGFR).
Gastrointestinal adverse reactions	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide and dulaglutide). In addition, gastrointestinal 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. Concomitant medication for nausea is permitted in the study. Additionally, PF-06882961 will be titrated from 10 mg BID dose to 120 mg BID over 28 days and from 120 mg BID to 200 mg BID over 16 days in the study.
Diabetic retinopathy complications	The potential risk is based on the product labeling for the injectable GLP-1R agonist semaglutide for type 2 diabetes mellitus. 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.
Suicidal ideation and behavior	The potential risk is based on the product labeling for the injectable GLP-1R agonist liraglutide for obesity. This risk has not been listed in the prescribing information for other marketed GLP-1R agonists for type 2 diabetes mellitus. There are no nonclinical or clinical data involving PF-06882961 to suggest an increased risk of suicidal ideation and behavior.	Suicidal ideation and behavior, along with symptoms of depression, will be monitored at frequent intervals during the study using the C-SSRS and PHQ-9 questionnaires, with referral to a mental health professional for further evaluation if needed.
Changes in heart rate and blood pressure	Increases in heart rate have been reported for marketed GLP-1R agonists, and increases in heart rate have been observed with PF-06882961 administration, with most HR values within the normal range. In addition, declines in systolic blood pressure have been noted at higher doses of PF-06882961.	Heart rate and blood pressure are monitored at frequent intervals during the clinical study.

Declines in body weight	Decreased appetite and body weight loss have been reported for marketed GLP-1R agonists, and declines in body weight have been noted at higher doses of PF-06882961.	A higher BMI was selected for inclusion criteria to minimize potential risk of body weight loss in the study population.
Acute gallbladder disease	The potential risk is based on the product labeling for the injectable GLP-1R agonist liraglutide for obesity and also exenatide. Acute gallbladder disease has not been observed in the PF-06882961 clinical trial program to date.	Participants with symptomatic gallbladder disease are excluded from this clinical study. Participants are monitored for AEs and laboratory tests that may suggest development of acute gallbladder disease.
Study Intervention: Rosuvastatin		
Skeletal muscle effects: These risks can occur at any dose level, but are increased at the highest dose (40 mg). Concurrent administration of some lipid-lowering therapies (fibrates or niacin) increases the risk of adverse skeletal muscle effects.	Risk based on product labeling.	Single dose of 10 mg is administered in the study and poses minimal risk. Other lipid-lowering therapies will not be administered as concomitant medications in this study.
Liver enzyme abnormalities.	Risk based on product labeling.	Single dose of 10 mg is administered in the study and poses minimal risk. Liver enzymes will be monitored throughout the study as part of the safety labs.
Study Intervention: Midazolam		
Respiratory depression	Risk based on product labeling.	A single dose of 2 mg is administered in the study and poses minimal risk. Participants will be monitored in an inpatient clinical research unit.
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

While PF-06882961 is not expected to provide any clinical benefit to otherwise healthy adult participants with obesity in this short-term study, potential benefits for participants in this study may include receiving medical evaluations/assessments associated with clinical study visits (eg, physical examinations, ECGs, Labs), and contributing to the process of developing a potential new therapy for T2DM.

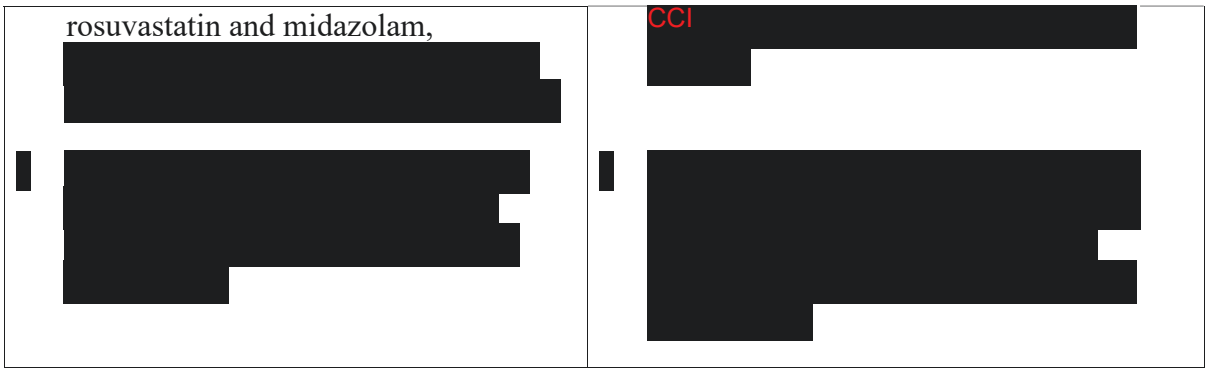
More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06882961 may be found in the IB, which is SRSD for this study.

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the effects of PF-06882961 on the pharmacokinetics of rosuvastatin in otherwise healthy adult participants with obesity. • To evaluate the effects of PF-06882961 on the pharmacokinetics of midazolam in otherwise healthy adult participants with obesity.	• Rosuvastatin plasma pharmacokinetic parameters: AUC_{inf} (if data permits* otherwise AUC_{last}) in Periods 1, 4 and 7. • Midazolam plasma pharmacokinetic parameters: AUC_{inf} (if data permits* otherwise AUC_{last}) in Periods 2, 5 and 8.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-06882961 administered separately and in combination with rosuvastatin or midazolam, in otherwise healthy adult participants with obesity.	• Assessment of treatment-emergent adverse events, clinical laboratory abnormalties, vital signs, body weight, and ECG parameters during the entire study. • Assessment of mental health as determined by C-SSRS and PHQ-9 during the entire study.
CCI [redacted]	[redacted]
[redacted]	[redacted]



* Should it be deemed that too few AUC_{inf} estimates (eg, less than 12 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary endpoint for CSR reporting. This will be considered for the rosuvastatin and midazolam objectives separately.

4. STUDY DESIGN

4.1. Overall Design

This study is a phase 1, open-label, 8-period, fixed-sequence study to evaluate the effect of PF-06882961, administered at two steady-state dose levels, on the pharmacokinetics of rosuvastatin and midazolam, administered separately as single doses, in otherwise healthy adult participants with obesity. Approximately 16 participants will be enrolled in the study.

Refer to Section 1.2 for study schema.

All participants will provide informed consent and undergo Screening evaluations to determine their eligibility. Screening will occur within 28 days of the first dose of study intervention on Day 1 of Period 1.

Participants will be admitted to the clinical research unit (CRU) on Day -1 of Period 1. The total duration of participation from the Screening Visit to the FU contact will be approximately 17 weeks ie, 117 days, of which up to 63 days will be inhouse (Period 1 (rosuvastatin): 5 days, Period 2 (midazolam): 2 days, Period 3 (PF-06882961): 29 days, Period 4 (PF-06882961+rosuvastatin): 4 days, Period 5 (PF-06882961 + midazolam): 1 day, Period 6 (PF-06882961): 16 days, Period 7 (PF-06882961+rosuvastatin): 4 days, Period 8 (PF-06882961 + midazolam): 2 days, FU visit 7-10 days from last dose study intervention and FU contact 28-35 days from last dose study intervention).

Participants may be discharged on Period 2, Day 2 and return to the CRU for Period 3, Day-1 within 7 days from discharge. Alternatively, participants may remain as inpatient on Period 2, Day 2 and begin Period 3, Day 1 activities the same day, without completing Period 3, Day -1 procedures. Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and Sponsor.

4.2. Scientific Rationale for Study Design

The purpose of this study is to characterize the effect of PF-06882961, administered at two steady-state dose levels, on the PK of single doses of rosuvastatin (10 mg) and midazolam (2 mg), administered separately, in adult participants with obesity. A multiple dose study will be conducted to ensure maximal clinically relevant steady-state PF-06882961 exposures are achieved. The drug-drug interaction effect will be initially assessed at PF-06882961 120 mg BID CCI [redacted] and again at 200 mg BID CCI [redacted]

Participants with a higher body mass index (BMI) range from 30.0 kg/m^2 to 45.4 kg/m^2 who are otherwise healthy will be enrolled to minimize potential clinical risk of body weight loss in this study and to target a similar BMI range as patients with T2DM. Adult participants with T2DM often have co-existing obesity and also require treatment for hyperlipidemia, and therefore it is likely that PF-06882961 may be co-administered with rosuvastatin in clinical practice. Rosuvastatin is a BCRP substrate with limited passive cellular membrane permeability, which makes it a probe substrate for both intestinal BCRP and liver BCRP. Intestinal BCRP acts as an efflux transporter limiting rosuvastatin absorption while liver BCRP actively excretes rosuvastatin into the bile. As PF-06882961 may be a BCRP inhibitor CCI [redacted] the effect of PF-06882961 at steady state on the PK of rosuvastatin is being assessed in this study. The elimination half-life of rosuvastatin is approximately 19 hours and therefore plasma sampling will be collected for rosuvastatin up to 96 hours after dosing.

Similarly, as PF-06882961 may be a time-dependent inhibitor of CYP3A4/5 CCI [redacted] the effect of PF-06882961 at steady state on the PK of midazolam, a CYP3A4/5 substrate, is being assessed in this study. Based on the turnover of CYP3A4/5,[12] steady state of CYP3A4/5 will be achieved with the repeated dosing of PF-06882961 120 mg BID and 200 mg BID. Midazolam is specifically metabolized by CYP3A4/5, and therefore the United States Food and Drug Administration (FDA) recommends the use of midazolam as the probe of choice for in vivo CYP3A4/5 drug metabolism and drug interaction studies. The elimination half-life of midazolam is approximately 2 hours and therefore plasma sampling will be collected for midazolam up to 24 hours after dosing.

CCI [redacted]

Clinical laboratory tests, assessments of vital signs, body weight, and 12-lead ECGs, physical examinations, and AE monitoring will provide data to evaluate the safety and tolerability of PF-06882961. Vital signs will be monitored at frequent intervals, as both increases in HR and mild decreases in systolic BP have been observed with PF-06882961 administration. As the degree of time-dependent inhibition of CYP3A4/5 is expected to be low, only minimal increases in midazolam exposure are expected and standard clinical monitoring of vital signs will be used in this study. Body weight will be measured at timepoints in the SoA, as GLP-1R agonists have been shown to decrease food intake and body weight. COVID-19 specific assessments have been incorporated to minimize the risks of COVID-19 related complications to participants and the study site personnel.

As part of the clinical safety laboratory tests, fasting blood glucose and HbA1c, will be used to assess changes in glycemic parameters in this study population. In addition, calcitonin, amylase, and lipase will be assessed, as these laboratory parameters have been shown to increase with marketed GLP-1R agonists.[13-16] In addition, thyroid stimulating hormone (TSH), free thyroxine (Free T4), lipids, coagulation profile and total bile acids (TBA) will be assessed, based on non-adverse findings in the nonclinical studies with PF-06882961. Assessment of Suicidal Ideation and Behavior (SIB) by Columbia Suicide Severity Rating Scale (C-SSRS)[17] and Patient Health Questionnaire 9 (PHQ-9)[18] will also be performed based on the potential risk related to the product labeling for the injectable GLP-1R agonist liraglutide in patients with BMI ≥30 kg/m^2.[16]

While GLP-1R agonists typically are not associated with hypoglycemia unless co-administered with anti-diabetic agents that can cause hypoglycemia (such as insulin or sulfonylureas), blood glucose concentrations will be monitored throughout the study via laboratory assessments, and monitoring of symptomatic hypoglycemic AEs (HAEs) will be performed. In addition, all participants will be instructed regarding the symptoms associated with, and management of, hypoglycemia, which will permit the monitoring of symptomatic HAEs.

Dosing of PF-06882961 (with or without rosuvastatin or midazolam) is planned to occur in the fed state, with standard breakfast and dinner, as this is the anticipated mode of administration in clinical use. Dosing of rosuvastatin and midazolam (with or without PF-06882961) is planned to occur in the fed state, with standard breakfast.

Females of childbearing potential may be enrolled into this study given the availability of embryo fetal developmental toxicity studies with PF-06882961. However, as marketed GLP-1R agonists, in addition to rosusvastatin, are listed as contraindicated in pregnancy, the use of a highly effective method of contraception is required and measures will be taken to limit the risk of pregnancy in the female population enrolled (see SoA and Appendix 4).

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

applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[19]

CCI [redacted]

4.3. Justification for Dose

PF-06882961: The DDI assessment will occur at two steady-state PF-06882961 dose levels, 120 mg BID and 200 mg BID.

The dose of PF-06882961 120 mg BID administered in this study represents the highest dose being assessed in the Phase 2b dose ranging study in T2DM. This dose was also administered in the Phase 1 C3421002 study and therefore will allow DDI assessment in this study at an anticipated exposure that was sufficiently tolerated. Based on data from the C3421002 study, the glucose lowering effect of PF-06882961 is expected to be similar to that of marketed GLP-1R agonists. CCI [redacted]

CCI [redacted] The titration to PF-06882961 120 mg BID is planned over 4 weeks (Section 6.1.1) and from 120 mg to 200 mg BID over 16 days, in increments of 20 mg every 4 days. These titration increments have been administered previously and are expected to be sufficiently tolerated.

Rosuvastatin: In a single dose escalation study, rosuvastatin was safe and well tolerated at doses up to 80 mg.[20] The most common AEs reported were headache and rash. There was no evidence of a relationship between the frequency of AEs and rosuvastatin dose. No serious adverse events (SAEs) were reported. Most DDI studies involving rosuvastatin as a substrate are conducted at the 10 mg or 20 mg dose level.[21-23] The therapeutic dose of rosuvastatin may be up to 40 mg. Since PF-06882961 is expected to increase rosuvastatin plasma exposure, ten (10) mg rosuvastatin was selected as the dose in the current study and is expected to be well-tolerated.

Midazolam: Midazolam has been administered at doses of 2-15 mg to assess CYP3A4/5 DDIs[12] and is currently recommended for clinical use as a single oral dose (0.25 to 1.0 mg/kg) or IV administration. Therefore, a single oral dose of midazolam 2 mg will provide measurable PK for 24 hours and is expected to be well-tolerated even if PF-06882961 results in an increase in midazolam plasma exposure.

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

The end of the study is defined as the date of the last visit (follow-up contact) of the last participant in the study.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female participants must be 18 to 65 years of age, inclusive, at the time of signing the ICD.

    - Women can be of child-bearing potential, however, cannot be pregnant, breastfeeding, or planning to become pregnant while participating in the study.

    - 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) ≥30.0 kg/m2 and not more than 45.4 kg/m2 at Screening.

4. Stable body weight, defined as <5 kg change (per participant report) for 90 days before Screening.

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

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

3. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg, contact with positive case, residence or travel to an area with high incidence) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

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

5. Known hypersensitivity to rosuvastatin or midazolam.

6. Diagnosis of type 1 or type 2 diabetes mellitus or secondary forms of diabetes at screening. **Note:** women with prior diagnoses of gestational diabetes *during pregnancy only* are eligible if they meet the other eligibility criteria.

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

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

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

10. Acute pancreatitis or history of chronic pancreatitis.

11. Symptomatic gallbladder disease.

12. Medical history or characteristics suggestive of genetic or syndromic obesity or obesity induced by other endocrinological disorders (eg, Cushing Syndrome).

13. History of major depressive disorder or history of other severe psychiatric disorders (eg, schizophrenia or bipolar disorder) within the last 2 years from screening.

14. Known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C, primary biliary cirrhosis, alcoholic liver disease, primary sclerosing cholangitis, autoimmune hepatitis, overlap syndrome, or prior known drug-induced liver injury.

15. History of HIV infection.

16. Any lifetime history of a suicide attempt.

Prior/Concomitant Therapy:

17. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.5 for additional details).

18. Systemic therapy with any of the medications that are moderate or strong CYP3A4/5, CYP2C9 and/or CYP2C19 inhibitors within 28 days or 5 half-lives (whichever is longer) or moderate or strong CYP3A, CYP2C9 and/or CYP2C19 inducers within 28 days or 5 half-lives (whichever is longer) prior to the first dose of rosuvastatin (Refer to Section 6.5 for additional details).

19. See Section 6.5 for prohibited prior/concomitant medications.

Prior/Concurrent Clinical Study Experience:

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

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

Diagnostic Assessments: At screening unless indicated

22. A Patient Health Questionnaire (PHQ-9) score ≥15 obtained at Screening or Day -1 in Study.

23. Response of "yes" to question 4 or 5, or on any behavioral question on the C-SSRS at Screening or Day -1 in Study.

24. A positive urine drug test.

25. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. BP should be measured in triplicate and the average of the 3 BP values should be used to determine the participant's eligibility. Note: At screening, the participant's arm circumference should be measured (eg, using a flexible anthropometric tape) at the midpoint of the length of the upper arm and the appropriate cuff selected and used throughout the study.

26. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate age- myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second or -third degree AV block, or serious bradyarrhythmias or tachyarrhythmias).

    If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

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

    - HbA1c ≥6.5%.
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level ≥2 times the upper limit of normal (ULN).
    - Total bilirubin level ≥1.5 times the ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.
    - TSH >1.5 times the ULN or <LLN.
    - Serum calcitonin > the ULN.

- Amylase or lipase > the ULN.
- Fasting blood glucose ≥126 mg/dL.
- Fasting C-peptide <0.8 ng/mL.
- Estimated glomerular filtration rate (eGFR) <80 mL/min/1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
- Positive testing for HIV, HepBsAg, or HCVAb. Study participants positive for HCVAb are to be excluded unless known to have been treated with a known curative therapy and negative for HCV RNA. Hepatitis B vaccination is allowed.
- A positive COVID-19 test.

Other Exclusions: At screening unless indicated

28. Participation in a formal weight reduction program (eg, Weight Watchers) within 90 days prior to Screening.
29. 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).
30. Current use of tobacco or nicotine containing products in excess of the equivalent of 5 cigarettes per day.
31. Known or suspected illicit drug use.
32. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing randomization (Day-1).
33. History of sensitivity to heparin or heparin induced thrombocytopenia if Hep-lock is used for IV blood draw.
34. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
35. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 8 hours prior to any safety laboratory and the morning predose PK evaluations (Periods 1-8).

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

- Participants should begin consumption of a standard breakfast (morning) and evening meal approximately 30 minutes prior to dosing. The breakfast and evening meal (dinner) will be consumed over approximately a 20 minute period, with the study intervention (PF-06882961) administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to complete the entire meal. Study intervention (PF-06882961) must be administered BID approximately 10 hours apart.

  Rosuvastatin or midazolam when administered alone will be given within approximately 10 minutes of completion of the morning meal.

  PF-06882961 will be administered first and the single dose of midazolam/rosuvastatin will be administered within 5 minutes of PF-06882961 for the periods where midazolam/rosuvastatin are co-administered with PF-06882961.

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

- Lunch will be provided approximately 4 hours after dosing with study intervention (PF-06882961). This applies to rosuvastatin and midazolam also.

- Dinner will be provided approximately 10 hours after dosing with study intervention. This applies to rosuvastatin and midazolam also.

- An evening snack may be permitted.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to Period 1 Day 1 until collection of the final PK blood sample on Period 8 Day 2.

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

5.3.2. Caffeine, Alcohol, and Tobacco

- Tobacco or nicotine use may be allowed according to CRU practices. Tobacco or nicotine use will not be permitted during frequent sampling procedures, and will not be permitted within 2 hours prior to any vital sign or ECG assessments. Tobacco or nicotine use will also not be permitted 2 hours before and 2 hours following any dose of study intervention. Tobacco or nicotine use must not exceed the limits specified in exclusion criterion for subjects who leave the CRU after Period 2 and return back for Period 3 of the study.

- Caffeine containing products will be permitted during the study with the following restrictions: caffeine containing products may not be consumed within 1 hour prior to measuring vital signs and ECGs.

- Participants will abstain from alcohol for 24 hours prior to admission to the clinical research unit (CRU) and continue abstaining from alcohol until collection of the final PK sample on Period 8 Day 2. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator. Intake of alcohol must not exceed the limits specified in exclusion criterion for subjects who leave the CRU after Period 2 and return back for Period 3 of the study.

5.3.3. Activity

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

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down for 4 hours after dosing in the morning on days of post-dose PK sample collections (except when required for BP, pulse rate, and ECG measurements).

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) 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 in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

A participant who qualified for this protocol but did not enroll within the 28-day screening window may be re-screened. In this situation, all screening procedures must be repeated and the participant assigned a new 8-digit study-specific study participant identification number (SSID) number. This criterion would also apply to participants who screened for this study more than 28 days prior to dosing.

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

10 mg, 40 mg, and 100 mg PF-06882961 Tablets will be supplied by Pfizer to the CRU in bulk along with individual dosing containers, as necessary, for unit dosing.

Commercially available oral rosuvastatin 10 mg tablets will be supplied by the CRU.

Commercially available midazolam oral syrup (2 mg/mL) will be supplied by the CRU.

6.1.1. Administration

Participants will receive PF-06882961 (morning dose), rosuvastatin or midazolam as applicable per SoA at approximately 0800 hours (plus or minus 2 hours). Participants will receive the evening dose of PF-06882961 approximately 10 hours after the morning dose of PF-06882961. Details on meals and dietary requirements and activity restrictions on dosing days are given in Section 5.3.

Investigator site personnel will administer PF-06882961, rosuvastatin, midazolam during each period (as applicable per SoA) with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

Administration of study intervention will occur according to the following Dosing Periods and Dosing Days, also listed in the SoA and Table 6.

Modification of dosing of PF-06882961 maybe permitted upon sponsor approval only. See Section 6.6.

Table 6. Dosing

Study Period	Days in Study	Drug & Dosage
Period 1, Day 1	1	Rosuvastatin 10 mg QD
Period 2, Day 1	5	Midazolam 2 mg QD
Period 3, Days 1-4	8-11	PF-06882961 10 mg BID
Period 3, Days 5-8	12-15	PF-06882961 20 mg BID
Period 3, Days 9-12	16-19	PF-06882961 40 mg BID
Period 3, Days 13-16	20-23	PF-06882961 60 mg BID
Period 3, Days 17-20	24-27	PF-06882961 80 mg BID
Period 3, Days 21-24	28-31	PF-06882961 100 mg BID
Period 3, Days 25-28	32-35	PF-06882961 120 mg BID
Period 4, Day 1	36	PF-06882961 120 mg BID + Rosuvastatin 10 mg QD
Period 4, Days 2-4	37-39	PF-06882961 120 mg BID
Period 5, Day 1	40	PF-06882961 120 mg BID + Midazolam 2 mg QD
Period 6, Days 1-4	41-44	PF-06882961 140 mg BID
Period 6, Days 5-8	45-48	PF-06882961 160 mg BID
Period 6, Days 9-12	49-52	PF-06882961 180 mg BID
Period 6, Days 13-16	53-56	PF-06882961 200 mg BID
Period 7, Day 1	57	PF-06882961 200 mg BID + Rosuvastatin 10 mg QD
Period 7, Days 2-4	58-60	PF-06882961 200 mg BID
Period 8, Day 1	61	PF-06882961 200 mg BID + Midazolam 2 mg QD

6.2. Preparation/Handling/Storage/Accountability

- 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.

- 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.

- 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.

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

- Study interventions should be stored in their original containers.

- 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.

- 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.

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.

Commercially available products rosuvastatin and midazolam provided by the CRU will be prepared as per the label and in accordance with the Protocol by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

The investigator will assign participant numbers to the participants as they are screened for the study. The first four digits of the SSID will reflect the sponsor-assigned site number and the remaining four-digits will reflect each participant's unique number assigned in chronological order as informed consent is obtained. In addition, on Day 1 of Period 1, each participant who is dosed with the investigational product will be assigned a separate, distinct, 2 digit number (as provided to the site by the Sponsor at the start of the study) to enable execution of Sponsors'standard processes for analysis of all PK-related samples.

In Periods 3 to 8, participants will receive the PF-06882961 doses as described in Table 7.

Table 7. PF-06882961 Dosing Regimens

Period & PF-06882961 Dose (dosed twice daily)	Number of PF-06882961 Tablets			Total Number of Tablets
	10 mg	40 mg	100 mg	
Period 3: 10 mg	1	-	-	1
Period 3: 20 mg	2	-	-	2
Period 3: 40 mg	-	1	-	1
Period 3: 60 mg	2	1	-	3
Period 3: 80 mg	-	2	-	2
Period 3: 100 mg	-	-	1	1
Period 3: 120 mg	2	-	1	3
Period 4: 120 mg	2	-	1	3
Period 5: 120 mg	2	-	1	3
Period 6: 140 mg	-	1	1	2
Period 6: 160 mg	2	1	1	4
Period 6: 180 mg	-	2	1	3
Period 6: 200 mg	-	-	2	2
Period 7: 200 mg	-	-	2	2
Period 8: 200 mg	-	-	2	2

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

Study participants will abstain from all concomitant treatments, except for the treatment of adverse events, as described in the Exclusion Criteria sections of this protocol.

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Systemic therapy with any of the medications that are moderate or strong CYP3A4/5, CYP2C9 and/or CYP2C19 inhibitors within 28 days or 5 half-lives (whichever is longer) or moderate or strong CYP3A, CYP2C9 and/or CYP2C19 inducers within 28 days or 5 half-lives (whichever is longer) prior to the first dose of rosuvastatin.

Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Anti-emetics (eg, prochlorperazine, promethazine, ondansetron) may be administered at the investigator's discretion with notification to the sponsor and entry in the CRF (See Section 6.5.1.1).

Sites are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

Hormonal contraceptives are not allowed to be used in participants who are WOCBP (see Appendix 4).

Females using hormonal contraceptives or taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. Depo-Provera® must be discontinued at least 6 months prior to the first dose of study treatment.

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 as listed in the SoA.

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

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-06882961; standard medical supportive care must be provided to manage the AEs, including administration of carbohydrates to treat HAEs (see Section 8.2.7).

6.5.1.1. Management of Nausea and Vomiting

Nausea and vomiting have been reported with administration of GLP-1R agonists and also with administration of PF-06882961 (see Section 2.2.4.1). Study participants complaining of nausea may be managed conservatively with bed rest and/or fluid management at the discretion of the investigator. If the nausea and vomiting are not amenable to conservative management, anti emetics (eg, prochlorperazine, promethazine, ondansetron) may be administered at the investigator's discretion with notification to the sponsor and entry in the CRF.

6.6. Dose Modification

If participants are not able to tolerate titration to higher doses of PF-06882961 (ie, ≥160 mg BID), titration to the next dose level may be delayed temporarily or titration to maximum tolerated dose may be permitted, with Sponsor approval only.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Criteria for a potential Hy's law case are met (see Appendix 6).
- Intent to become pregnant or pregnancy confirmed by serum beta human chorionic gonadotropin (β-hCG) testing.
- Safety or tolerability concern arises, in particular if not responsive to symptomatic management, dosing with study intervention may be stopped in an individual participant at investigator discretion;
- Based on mental health assessment as outlined in Section 8.2.5, should be discontinued from dosing at investigator discretion.
- If the criteria for permanent discontinuation are met, the site should notify the sponsor Medical Monitor or sponsor Clinician.

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

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

ECG Changes

See Appendix 7 for additional guidance of ECG findings of potential clinical concern.

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.
- Safety or behavioral reasons at the discretion of the investigator, including reasons related to mental health assessments as described in Section 8.2.5.

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

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

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 attend a required study visit:

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

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.

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.

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 556 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.

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

Complete physical exam will be done at time points specified in the SoA otherwise, brief exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.

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. Height will be measured at screening only. Weight will be recorded using a calibrated scale (with the same scale used if possible for the duration of the study) reporting weight in either pounds (lb) or kilograms (kg), and accuracy to the nearest 0.2 lb (or 0.1 kg); ie, the device must be able to distinguish a difference between 150.4 lb (68.4 kg) versus 150.2 lb (68.3 kg). The scale must be placed on a stable, flat surface.

Weight measurement should be taken under the following conditions:

- In the morning in a fasting state.
- After void of urine.
- After removal of shoes, bulky layers of clothing and jackets so that only light clothing remains.
- Remove the contents of their pockets.
- While remaining still during the measurement.

8.2.2. Vital Signs

Vital signs (systolic BP, diastolic BPand pulse rate) will occur as specified in the SoA. Supine-BP will be measured with the participant’s arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of supine rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be

instructed not to speak during measurements. When triplicate measurements are obtained, they should be collected approximately 2 minutes apart.

At screening, the participant's arm circumference should be measured (eg, using a flexible anthropometric tape) at the midpoint of the length of the upper arm and the appropriate cuff selected and used throughout the study. 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.

See Appendix 8 for proposed chronology of procedures for nominal time points when vital sign assessments coincide with other procedures.

8.2.2.1. Temperature

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

8.2.3. Electrocardiograms

Standard 12-lead ECGs 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 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 screening measurements. Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥60 msec from the screening **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 ≥30 msec from the screening **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 QTc 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 28-35 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

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

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

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

8.2.5.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an interview based rating scale to systematically assess suicidal ideation and suicidal behavior.[17] The "baseline/screening" version of the C-SSRS will be administered at Screening and Day -1 in study. Participants who respond "yes" to Question 4 or 5 (indicating suicidal ideation), or to any suicidal behavioral question on the C-SSRS at screening or Day-1 will not be permitted in the study (see Section 5.2). The "since last visit" version of the C-SSRS will be administered at the time points specified in the SoA. The C-SSRS will be administered by study site staff who have completed training in its administration.

8.2.5.1.1. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the guidance document provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.2.5.2. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9[20] is a 9 item self-report scale for the assessment of depressive symptoms.[18] The PHQ-9 will be completed by participants and reviewed by site staff at the pre-defined time points outlined in the SoA. A PHQ-9 score of ≥15 at Screening and Day -1 indicates clinically significant depression and serves as an exclusion criterion for this study (see Section 5.2).

8.2.5.3. Referral to a Mental Health Professional

A participant should be referred to a MHP for the following reasons:

- Response of "yes" to question 4 or 5, or on any behavioral question on the C-SSRS.
- A score of ≥15 on the PHQ-9.
- In the investigator's judgment a risk assessment or exclusion is required.

A clinically-qualified MHP is a MHP with appropriate training in the assessment of suicide risk, according to local clinical practice standards and regulations, who would normally evaluate the risk for suicidal ideation and behavior in a patient.

Participants who have recurrent suicidal ideation or behavior during the study should be discontinued from the study and treated appropriately. If a study participant endorses a 4 or 5 on the ideation subscale or any behavioral item of the C-SSRS on two or more occassions and is confirmed to have active suicidal ideation or behavior on both occasions by a risk assessment conducted by a qualified MHP, then the participant should be discontinued from the study and treated appropriately.

Participants who meet criteria for referral to a MHP, but refuse evaluation and/or treatment by a MHP, must be assessed by the investigator to determine if the participant should be discontinued from dosing or from the study.

8.2.6. Pregnancy Testing

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

8.2.7. Management of Hypoglycemia

While hypoglycemia is not expected in the study participants, fasting blood glucose will be measured as part of laboratory assessment per the SoA. In addition, as a precaution, participants will be monitored for the signs and symptoms associated with hypoglycemia.

Any episode of hypoglycemia must be captured on the HAE CRF with specific details captured on the HAE Form CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.2.7.1 below.

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

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

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

HAE is defined as **one** of the following:[24]

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/local laboratory (blood 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/local 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 one of the following neurological symptoms:

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

3. Either:

    - If blood glucose was measured and was ≤54 mg/dL (2.7 mmol/L) using glucometer (or central/local 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.

8.2.8. Glucometer Monitoring of Glucose

Monitoring of fingerstick blood glucose (FSBG) using glucometer measurements is not required per protocol, but may be obtained if the investigator or participant notes symptoms of hypoglycemia.

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

If an FSBG result is ≤70 mg/dL, a second FSBG should be obtained to confirm the glucose value, in addition to a venous sample that will be sent to the clinical laboratory for confirmation. If the value from this second FSBG is also ≤70 mg/dL, the second value will be recorded as a hypoglycemic AE. FSBG will continue to be monitored until the glucose value returns to >70 mg/dL. Samples may be taken more frequently if deemed necessary by the investigator.

8.2.9. COVID-19 Specific Assessments

Participants will be pre-screened for COVID-19 related symptoms and risks[25,26] and tested for SARS-CoV-2 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4 x 24 hours in house), or if they develop COVID-19 like symptoms.

Additional testing may be conducted as required by local regulations or by the Principal Investigator. Results must be negative for admission to the CRU.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

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

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

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

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

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion.

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Cardiovascular and Death Events

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

Not Applicable.

8.3.9. Medical Device Deficiencies

Not Applicable.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Not Applicable.

8.3.9.2. Follow-up of Medical Device Deficiencies

Not Applicable.

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Not Applicable.

8.3.9.4. Regulatory Reporting Requirements for 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.**

Other examples include, but are not limited to:

- The administration of expired study intervention.
- The administration of an incorrect study intervention.
- The administration of an incorrect dosage.
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

8.4. Treatment of Overdose

For this study, any dose of PF-06882961 greater than 600 mg within a 24-hour time period will be considered an overdose.

For this study, overdose for rosuvastatin[10] and midazolam[11] will be per the USPI label.

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

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of 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 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

8.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of rosuvastatin, midazolam [redacted] as specified in the SoA.

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 study intervention 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 [redacted]

Samples collected for measurement of plasma concentrations of study intervention will be analyzed using a validated analytical method in compliance with applicable SOPs. [redacted]

Genetic analyses will not be performed on these samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

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

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5.1. PK of Rosuvastatin

Samples will be used to evaluate the PK of rosuvastatin. Blood samples of approximately 5 mL, to provide a minimum of plasma volume of 2 mL, will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) for measurement of plasma concentrations of rosuvastatin 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.

CCI [redacted]

8.5.2. PK of Midazolam

Samples will be used to evaluate the PK of midazolam. Blood samples of approximately 2 mL, to provide a minimum of plasma volume of 0.8 mL, will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) for measurement of plasma concentrations of midazolam 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.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

8.6. Pharmacodynamics

Not applicable.

CCI

CCI

CCI

CCI

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

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

9.2. Sample Size Determination

A sample size of approximately 16 participants will be enrolled such that approximately 12 evaluable participants complete the study. This minimum number of evaluable participants has been selected to provide sufficient precision to detect a 1.25-fold difference in AUC_{inf} for either rosuvastian or midazolam as described below.

The primary comparisons of interest are as follows:

- For rosuvastatin AUC_{inf}:
  - The co-administration of rosuvastatin and PF-06882961 120 mg BID (Period 4) versus rosuvastatin alone (Period 1, reference treatment).
  - The co-administration of rosuvastatin and PF-06882961 200 mg BID (Period 7) versus rosuvastatin alone (Period 1, reference treatment).
- For midazolam AUC_{inf}:
  - The co-administration of midazolam and PF-06882961 120 mg BID (Period 5) versus midazolam alone (Period 2, reference treatment).
  - The co-administration of midazolam and PF-06882961 200 mg BID (Period 8) versus midazolam alone (Period 2, reference treatment).

The expected widths of the 90% confidence intervals with 80% coverage probability for these comparisons are shown in Table 8, for a range of possible effects based on a sample size of 12 participants.

Table 8. Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects and Parameters of Interest

Parameter	Estimated Effect (Test/Reference)	AUC_{inf}	
		Probable 90% CI	Probable CI Width
AUC_{inf} (Rosuvastin or Midazolam)	75%	60 to 94%	34%
	100%	80 to 125%	45%
	125%	100 to 156%	56%
	150%	120 to 187%	67%
	200%	160 to 250%	89%

These estimates are based on an assumed conservative standard deviation of 0.284 (equivalent to a geometric coefficient of variation of 29%) in $\log_e AUC_{inf}$ for both rosuvastatin and midazolam. These estimates are based on data from previous internal DDI studies of rosuvastatin or midazolam.

9.3. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Evaluable	All participants assigned to study intervention and who take at least 1 dose of study intervention.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.
PK Concentration Set	The PK concentration population is defined as all participants who received at least 1 dose of Rosuvastastin, midazolam and/or PF-06882961 and in whom at least 1 plasma concentration value is reported.

Participant Analysis Set	Description
PK Parameter Set	The PK parameter analysis population is defined as all participants who received at least 1 dose of rosuvastatin, midazolam and/or PF-06882961 and have at least 1 of the PK parameters of interest calculated. Should vomiting occur after co-administration of rosuvastatin/midazolam with PF-06882961, the resulting PK parameters from that participant from the corresponding period may be excluded, where further details will be provided in the SAP.

9.4. Statistical Analyses

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

9.4.1. General Considerations

9.4.1.1. Derivation of Pharmacokinetic Parameters

The plasma PK parameters for rosuvastatin and midazolam following single dose administration (either alone or in co-administration with PF-06882961) will be derived from the concentration-time profiles as detailed in Table 9 below. CCI [redacted]

Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 9. Plasma PK Parameters for Rosuvastatin and Midazolam

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.
CCI	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

* as data permit.

CCI [redacted]

[redacted]

9.4.2. Statistical Methods for Pharmacokinetic data

The PK data for rosuvastatin, midazolam CCI [redacted] will be analyzed and reported separately.

Plasma concentrations will be listed and summarized descriptively by PK sampling time and treatment (dosing alone vs. co-administration or dose, as applicable). Individual participant and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used for plasma samples. Median profiles will be presented on both linear-linear and log-linear scales.

Natural log-transformed AUC_{inf} (as data permit) of rosuvastatin administered alone or co-administered with PF-06882961 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-reference) and corresponding 90% confidence intervals will be obtained from the models. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. The two test treatments will be 'rosuvastatin and PF-06882961 120 mg BID' (Period 4) and 'rosuvastatin and PF-06882961 200 mg BID' (Period 7), which will be reported separately in comparison to

the reference treatment of 'rosuvastatin alone' (Period 1). The same analysis for natural log-transformed CCI AUC_{last} of rosuvastatin will also be conducted.

Natural log_e-transformed AUC_{inf} (as data permit), CCI and AUC_{last} of midazolam administered alone or co-administered with PF-06882961 will be analyzed and reported separately using the same mixed effect model as described above for rosuvastatin. The two test treatments will be 'midazolam and PF-06882961 120 mg BID' (Period 5) and 'midazolam and PF-06882961 200 mg BID' (Period 8), which will be reported separately in comparison to the reference treatment of 'midazolam alone' (Period 2).

In the event that less than 12 participants have PK parameters related to co-administration with PF-06882961 200 mg BID, the above mixed effect models may additionally/alternatively include PK parameters from the maximum tolerated dose of PF-06882961 (if applicable), where further details will be included in the SAP.

The above and other PK parameters for rosuvastatin and midazolam CCI [redacted] will be separately summarized descriptively by treatment.

9.4.3. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, body weight 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.

9.4.3.1. Electrocardiogram Interval Analyses

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

CCI [redacted]

CCI [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

CCI [redacted]

[redacted]

[redacted]

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 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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may

withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

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

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

10.1.8. Study and Site Start and Closure

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

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

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

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

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

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

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

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the SToD Team Roster.

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 11. Protocol Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST ALT Total bilirubin Direct bilirubin Indirect bilirubin GGT Alkaline phosphatase Uric acid Albumin Total protein	Urinalysis: • pH • Glucose (qual) • Protein (qual) • Blood (qual) • Ketones • Nitrites • Leukocyte esterase • Urobilinogen • Urine bilirubin • Microscopy[a]	HbA1c Serum pregnancy test (β-hCG)[b] Lipid panel: • Total cholesterol • Direct LDL-C • HDL-C • Triglycerides TSH Free T4 Calcitonin Amylase Lipase ***Serum*** total bile acids PT/INR/aPTT COVID-19 test Urine drug screening[c] <u>Screening only:</u> FSH[d] C-peptide (fasting) HIV HepBsAg HCVAb HCV RNA
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin		

	Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

b. Serum β-hCG for all WOCBP.

c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific). At screening, Period 1 Day-1, Period 3 Day-1 and at the discretion of the investigator.

d. For all female participants to confirm post-menopausal status only.

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CO2 = carbon dioxide; COVID-19 = corona-virus disease 2019; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; GGT = gamma-glutamyl transferase; HbA1c = glycated hemoglobin; HCVAb = Hepatitis C Virus Antibody; HCV RNA = Hepatitis C Virus RNA; HDL-C = high density lipoprotein cholesterol; HepBsAg = Hepatitis B Surface Antigen; HIV = Human Immunodeficiency Virus; INR = international normalized ratio; LDL-C = low density lipoprotein cholesterol; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; qual = qualitative; RBC = red blood cell; THC = Tetrahydrocannabinol; TSH = thyroid stimulating hormone; WBC = white blood cell; WOCBP = women of child bearing potential.

Investigators must document their review of each laboratory safety report.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored. CCI [redacted] These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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 Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:

  - Is associated with accompanying symptoms.

  - Requires additional diagnostic testing or medical/surgical intervention.

  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.

- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.3.2. Definition of SAE

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

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

baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording/Reporting

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

occupational exposure.

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

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

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

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

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will

be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.

- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

OR

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

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

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
     - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
     - Female on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

1. Intrauterine device.
2. Bilateral tubal occlusion.
3. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

Sexual abstinence.

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

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

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

CCI

[redacted]

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

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

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

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

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

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

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

ECG Findings That Qualify as SAEs

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

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

10.8. Appendix 8: Proposed Chronology of Procedures

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

- 12 lead ECG: obtain prior to vital signs assessment, blood samples, and prior to dosing (as applicable for pre-dose collection) (see Section 8.2.3);
- Vital Signs (BP, PR): obtain after 12 lead ECG collection but prior to obtaining blood samples and prior to dosing (as applicable for pre-dose collection) (see Section 8.2.2);
- Temperature: obtain after 12 lead ECG collection but prior to obtaining blood samples and prior to dosing (as applicable for pre-dose collection) (see Section 8.2.2.1);
- Fasting blood samples [for safety (see Section 8.2.4, PK (see Section 8.5), CCI [redacted] after assessment of 12 lead ECG and vital signs but prior to dosing (as applicable for pre-dose collection);
- For the post-dose PK blood collections (see Section 8.5): if collection time coincides with time of a meal/snack, these blood samples should be collected just prior to the meal/snack;
- Other pre-dose procedures: obtain sample/perform procedure as close as possible to the scheduled time, but may be obtained before or after blood sample collection(s);
- Dosing: must occur with the morning meal; and where applicable, after any pre-dose blood sample collection(s).

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time.
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})
$AUC_{\tau 1}$	area under the plasma concentration-time profile where τ_1 = 0 to 10 hours
CCI [redacted]	[redacted]
AV	atrioventricular
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
cAMP	3'-5'-cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CCI [redacted]	[redacted]
C_{last}	predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
CCI [redacted]	[redacted]
CO2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial

Abbreviation	Term
%CV	percent coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ET	early termination
$E_{udra}CT$	European Clinical Trials Database
FDA	Food and Drug Administration
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide 1
GLP-1 R	glucagon-like peptide 1 receptor
HAE	hypoglycemic adverse event
HbA1c	hemoglobin A_{1c}
HepBsAg	hepatitis B surface antigen
HCV	Hepatitis C virus
HCVAb	hepatitis C antibody
HDL-C	high density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IR	immediate release
IRB	Institutional Review Board
IV	intravenous

Abbreviation	Term
IVGTT	intravenous glucose tolerance test
K_I	apparent inactivation constant at half-maximal rate of inactivation
k_{inact}	maximal inactivation rate ()
K2EDTA	dipotassium ethylenediaminetetraacetic acid
LBBB	left bundle branch block
LDL-C	low density lipoprotein cholesterol
LFT	liver function test
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	Multidrug resistance
MEN2	multiple endocrine neoplasia syndrome type 2
MHP	mental health professional
msec	millisecond
MTC	medullary thyroid carcinoma
N/A	not applicable
NOAEL	no-observed-adverse-effect level
OATP	organic anion transporting polypeptides
OCT	organic cation transporter
PD	pharmacodynamic(s)
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic(s)
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	Once a day
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
R_{ac}	mean ratios based on dose normalized AUC_{24}
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SSID	study-specific subject identification
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Term
CCI	[redacted]
T2DM	type 2 diabetes mellitus
T4	thyroxine
TBA	total bile acids
TBili	total bilirubin
TEAEs	treatment emergent adverse events
THC	tetrahydrocannabinol
CCI	[redacted]
TSH	thyroid stimulating hormone
UGT	uridine 5'-diphospho glucuronosyltransferase glucuronosyltransferase
ULN	upper limit of normal
US	United States
USPI	United States package insert
CCI	[redacted]
WBC	white blood cell
WOCBP	woman of childbearing potential

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