A PHASE 1, OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETIC INTERACTIONS BETWEEN PF-06882961 AND PF-06865571 IN HEALTHY ADULT PARTICIPANTS (PART A) AND OVERWEIGHT ADULTS OR ADULTS WITH OBESITY WHO ARE OTHERWISE HEALTHY (PART B)

Study Intervention Number:	PF-06882961 and PF-06865571
Study Intervention Name:	N/A
US IND Number:	CCI
EudraCT Number:	N/A
Protocol Number:	C3421038
Phase:	1

Short Title: A Phase 1 Study to Evaluate the Pharmacokinetic Interactions Between PF-06882961 and PF-06865571

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol Amendment #2	03 June 2021	Section 1 – Protocol Summary – Objectives and Endpoints, Schedule of Activities – Part B, Section 2.2.4.2.1 – Clinical Pharmacokinetics of PF-06882961, Section 3 – Objectives and Endpoints, Section 4.2 – Scientific Rationale for Study Design, Section 8.8 Biomarkers, Section 9.4 – Statistical Analyses: Added plasma CP-I and 4-β-hydroxycholesterol/cholesterol assessments at specified timepoints in Part B and updated the background, study rationale, objectives/endpoints, assessments/procedures and statistical analyses as appropriate. Rationale: Preliminary draft data from study C3421007 indicate that a decrease in exposure of midazolam are observed when co-administered with PF-06882961. To investigate the mechanism of this interaction, assessment of plasma 4-β-hydroxycholesterol/cholesterol, an endogenous probe for CYP3A induction, is being added in Part B. In vitro studies indicate PF-06882961 may inhibit OATP1B1 at dose(s) evaluated in this study. Therefore, to evaluate this potential effect of PF-06882961, measurement of plasma CP-I, an endogenous probe for OATP1B activity, is being added in Part B. Schedule of Activities Part B, Section 4.2 – Scientific Rationale for Study Design, Table 14 – Protocol Required Safety Laboratory Assessments: Added Cystatin-C sampling at baseline and subsequent safety laboratory assessments.

		Rationale: PF-06865571 is a dose-dependent inhibitor of the transporters OCT2/MATE in the kidney. As expected, increases in serum creatinine without a change in renal function (as assessed via eGFR determined using Cystatin-C) have been noted in prior studies. This interaction interferes with accurate monitoring of renal function with serum creatinine; therefore, Cystatin-C sampling is being introduced for Part B to enable accurate monitoring of renal function as part of safety assessments during repeated co-administration of PF-06865571 and PF-06882961. Section 2.2.4.1.1 – Clinical and Safety Experience with PF-06882961: Added preliminary safety data from the C3421007 study. Rationale: The C3421007 preliminary data provides the most up-to-date clinical safety data with PF-06882961. Section 5.4 – Screen Failures: Modified rescreening criteria to clarify that repeating of screening procedures and reassignment of new identification number is not required in the event of unexpected delays as long as laboratory results obtained prior to first dose administration meet eligibility criteria. Rationale: This was an inadvertent inconsistency between rescreening language in Section 5.4 – Screen Failures and Section 8 – Study Assessments and Procedures. Updated language allows for flexible rescreening procedures within a healthy volunteer population. Section 8 – Study Assessments and Procedures: Modified blood sampling volume

		from 400 mL rounded up to 525 mL for Part B. Rationale: Cystatin-C assessments require an additional 55 mL total blood sampling volume. CP-I and 4-β-hydroxycholesterol/cholesterol assessments require 51 mL and 16 mL blood sampling volume, respectively.
Protocol Amendment #1	12 March 2021	Section 1.1 - Synopsis, Section 4.1.1 - Part A Study Design; The duration of Part A is approximately 9 weeks instead of 8 weeks. Rationale: This was an inadvertent miscalculation of the number of weeks within the study timeline in FAP. Section 1.1 - Synopsis, Section 3 - Objectives and Endpoints: Included "Assessment of mental health as determined by C-SSRS and PHQ-9 in Part B of the study" as secondary endpoint in Part B. Rationale: This was an inadvertent exclusion in FAP. Schedule of Activities Part A: Removed 'X' from 'Inpatient stay at CRU' row for the ET/DC visit. Rationale: Table is now consistent with the Schedule of Activities in Part B. The Early Termination/Discontinuation visit is considered out-patient and does not require an overnight inpatient stay. Schedule of Activities Part A: Ensured footnotes for Day -1 activities were footnote 'e' "If participant is not discharged from the CRU between Periods 1 and 2, procedure only needs to be conducted in Period 1 only."

		Rationale: Error during protocol amendment formatting/finalization. Schedule of Activities Part A/B, Section 4.2 - Scientific Rationale for Study Design, Section 8, Study Assessments and Procedures, CCI [redacted] Rationale: Updated terminology with new protocol/ICD templates. Schedule of Activities Part A/B, Appendix 2-Clinical Laboratory Tests: Removed HepBsAb and HepBcAb from Screening testing. Rationale: Removal ensures consistency with Exclusion Criteria #27 and C3421007 eligibility criteria. Sampling was confirmed not to be necessary for determination of viral exclusionary status. Section 5.2-Exclusion Criteria #2: Removed appendectomy from list of any condition possibly affecting drug absorption. Rationale: It was determined that appendectomy would not affect drug absorption and its inclusion was an oversight. Section 5.2-Exclusion Criteria #19: Added language that an emergency use authorized or approved COVID-19 vaccine is considered a concomitant medication.

		Rationale: Included COVID-19 vaccine language in clinical studies as per FDA guidance. Section 5.2-Exclusion Criteria #27: Modified and added additional abnormalities in clinical laboratory tests, including ALT/AST, total bilirubin, TSH, fasting triglyceride, INR, and PLT. Rationale: FDA correspondence from IND submission. Section 10.1.7 - Source Documents: Added language for data types that may be recorded directly on the CRFs (ie, for which there is no existing written or electronic record of data) and is to be considered data source. Rationale: Allow for direct data capture CRF input, reducing the amount of data transcribed from paper source documents to improve efficiency and data quality. Section 6.7 - Stopping Rules: Added section and sub-section 6.7.1-6.7.3 to call out stopping rules for participant death, development of adverse events, and individual participant development of adverse events. Rationale: FDA correspondence from IND submission. Section 9.4.3 - Safety Analyses: Continuous cardiac monitoring removed from items to be reviewed and summarized. Rationale: This was an inadvertent exclusion in FAP. Continuous cardiac monitoring/telemetry was never being performed in this study. Section 9.4.3.1 - Electrocardiogram Analyses: Added sentence that exposure-QT analyses is

		performed, it will be reported separately, not as part of the CSR. Rationale: Clarifcation as requested. Appendix 1, Section 10.1.3 - Informed Consent Process: Removed last paragraph in section describing consent for optional additional research. Rationale: Removed as per new ICD/protocol template guidance and language. Appendix 4, Section 10.4.3 - Woman of Childbearing Potential, Section 10.4.4 - Contraception Methods: Use of hormonal contraception by WOCBP or females whose menopausal status is in doubt has been removed. Rationale: Per study team discussion, use of hormonal contraception has been removed from this study to ensure no possible drug-drug interactions with study interventions and to maintain consistency with Section 6.5. Appendix 9, Alternative Measures During Public Emergencies: Added this appendix. Rationale: Includes new template content, re-affirming COVID-19 testing eligibility and COVID-19 safety reporting. Other minor spelling errors and inconsistencies corrected/modified throughout protocol to ensure accuracy and improved trial conduct.
Original protocol	23 December 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 Study to Evaluate the Pharmacokinetic Interactions Between PF-06882961 and PF-06865571

Rationale: This study will evaluate the PK interactions between PF-06882961 and PF-06865571 in healthy adult participants (Part A) and overweight adults or adults with obesity who are otherwise healthy (Part B).

Objectives and Endpoints:

Objectives	Endpoints
Part A	
Primary:	**Primary:**
• To evaluate the effects of PF-06865571 on the single-dose pharmacokinetics of PF-06882961 in healthy adult participants.	• PF-06882961 plasma pharmacokinetic parameters: C_{max} and AUC_{24}.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-06882961 alone and in combination with PF-06886571 when administered to healthy adult participants.	• Assessment of treatment-emergent adverse events, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters during the entire study.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To evaluate the effects of PF-06865571 on additional pharmacokinetic parameters of PF-06882961 in healthy adult participants.	• Additional PF-06882961 plasma pharmacokinetic parameters: T_{max}.
Part B	
Primary:	**Primary:**
• To evaluate the effects of PF-06882961 on the single-dose pharmacokinetics of PF-06865571 in overweight adults or adults with obesity who are otherwise healthy. • To evaluate the effects of PF-06865571 on the multiple-dose pharmacokinetics of PF-06882961 in overweight adults or adults with obesity who are otherwise healthy.	• PF-06865571 plasma pharmacokinetic parameters on Day 1 and Day 47: C_{max}, AUC_{last}, and $AUC_{inf,}$ as data permits. • PF-06882961 plasma pharmacokinetic parameters on Day 46 and Day 61: C_{max} and AUC_{12}.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-06882961 and PF-06865571 when administered separately and in combination in overweight adults or adults with obesity who are otherwise healthy.	• Assessment of treatment-emergent adverse events, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters during the entire study. • Assessment of mental health as determined by C-SSRS and PHQ-9 in Part B of this study.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To evaluate the effects of PF-06882961 on additional pharmacokinetic parameters of PF-06865571 in overweight adults or adults with obesity who are otherwise healthy.	• Additional PF-06865571 plasma pharmacokinetic parameters on Day 1 and Day 47: T_{max}, CL/F, V_z/F, and $t_{½}$, as data permits.

• To evaluate the effects of PF-06865571 on additional pharmacokinetic parameters of PF-06882961 in overweight adults or adults with obesity who are otherwise healthy.	• Additional PF-06882961 plasma pharmacokinetic parameters on Day 46 and Day 61: T_{max} and CL/F.
CCI	
• To evaluate the effects of PF-06882961 on the multiple-dose pharmacokinetics of PF-06865571 in overweight adults or adults with obesity who are otherwise healthy.	• PF-06865571 plasma pharmacokinetic parameters on Day 61: C_{max}, T_{max}, and AUC_{12}.
• To evaluate the effects of multiple doses of PF-06882961 on CYP3A induction in overweight adults or adults with obesity who are otherwise healthy.	• Morning pre-dose 4-β-hydroxycholesterol/cholesterol plasma ratio on Days 1, 19, 31, and 47.
• To evaluate the effect of multiple doses of PF-06882961 on CP-I in overweight adults or adults with obesity who are otherwise healthy.	• CP-I parameters on Days 30 and 46: AUC_{12} and C_{max}.

Overall Design: This study will be conducted in 2 parts. Part A is an open-label, two-period, two-sequence, crossover cohort investigating the potential effect of PF-06865571 on the PK of PF-06882961 in healthy adult participants. Part B is an open-label, fixed-sequence cohort to evaluating the effect of PF-06882961 on the PK of PF-06865571, as well as the effect of PF-06865571 on the PK of PF-06882961 in overweight adults or adults with obesity who are otherwise healthy. The effect of PF-06882961 on PF-06865571 PK will be evaluated at steady-state 200 mg BID doses of PF-06882961. Then, PF-06882961 and PF-06865571 will be coadministered for approximately 2 weeks for further evaluation of PK interactions and to generate additional safety and tolerability data on the combination.

Number of Participants: A cohort of approximately 8 participants will be enrolled in Part A. Approximately 16 participants will be enrolled in Part B such that approximately 12 evaluable participants complete Part B.

Intervention Groups and Duration: The study interventions in this study are PF-06882961 and PF-06865571. Both will be administered as tablets for oral administration. In Part A, each participant will receive a single dose of PF-06882961 in 1 period and co-administration of PF-06882961 and PF-06865571 in another period. The duration of Part A will be approximately 9 weeks. In Part B, each participant will receive PF-06865571 alone, PF-06882961 alone, and co-administration of PF-06865571 and PF-06882961. The duration of Part B will be approximately 18 weeks.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods: In Part A, natural log-transformed C_{max} and AUC_{24} of PF-06882961 administered alone or co-administered with PF-06865571 will be analyzed using a mixed effect model with treatment, sequence, and period as fixed effects and participant embedded in sequence as a random effect to evaluate the effect of PF-06865571 on PF-06882961 PK.

To quantify the effect of PF-06882961 on PF-06865571 PK in Part B, natural log-transformed C_{max}, AUC_{last}, and AUC_{inf} (as data permit) of PF-06865571 300 mg administered alone or in combination with PF-06882961 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Similarly, to quantify the effect of PF-06865571 on PF-06882961 PK, natural log-transformed C_{max} and AUC_{12} of PF-06882961 200 mg BID administered alone or in combination with PF-06865571 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. All safety data will be summarized descriptively through appropriate data tabulation, descriptive statistics, categorical summaries, and graphical presentations.

1.2. Schema

1.2.1. Treatment Scheme for Part A

	Period 1	Washout*	Period 2
Sequence 1 (n=4)	Treatment A: 20 mg PF-06882961 single dose	Washout of at least 3 days*	Treatment B: 20 mg PF-06882961 single dose plus 300 mg PF-06865571 single dose
Sequence 2 (n=4)	Treatment B: 20 mg PF-06882961 single dose plus 300 mg PF-06865571 single dose	Washout of at least 3 days*	Treatment A: 20 mg PF-06882961 single dose
*Each participant is planned to undergo 2 treatment periods with a washout interval between periods of at least 3 days following the final dose of study intervention administered in Period 1.			

1.2.2. Treatment Scheme for Part B

	Period 1	Period 2	Period 3	Period 4
	Days 1-2	**Days 3-46**	**Days 47-48**	**Days 49-62**
PF-06865571 (DGAT2) Dose	300 mg single dose on Day 1 only[a]	N/A	300 mg single dose on Day 47 only[a]	300 mg BID on Days 49-61[a]
PF-06882961 (GLP-1) Dose	N/A	10 mg BID titrated to 200 mg BID[b,c]	200 mg BID[c]	200 mg BID on Days 49-61[b,c]

a. Dense PK sampling for measurement of PF-06865571 plasma concentrations on Day 1 (reference), Day 47 (test), and Day 61 (summary statistics only).

b. Dense PK sampling for measurement of PF-06882961 plasma concentrations on Day 46 (reference) and Day 61 (test).

c. Doses of PF-06882961 may be reduced based on PK results of Part A of this study and safety and tolerability results of Study C3421007.

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.

1.3.1. Schedule of Activities for Part A

Table 1. Part A – Overall Schedule of Activities

Visit Identifier[a]	Screen Day -28 to -2	Periods 1 and 2[b]												ET/DC	F/U[c]
		Day -1	Day 1										Day 2		
Hours After Dose			0	0.5	1	2	3	4	6	8	10	12	16	24		
Informed consent & demography	X															
Outpatient visit (after ≥10 h fast)	X															
COVID-19 questionnaire[d]	X	X[e]														
COVID-19 testing[f]	X	X														
COVID-19 temperature check[g]	X	X	X[h]											X	X	
Inpatient stay at CRU		X	→	→	→	→	→	→	→	→	→	→	→	X[i]		
Assessment of eligibility (with update on Day-1 in Period 1 only)	X	X														
Medical and medication history	X	X[e]														
Review alcohol, tobacco, and drug use	X	X[e]														
Review prior or concomitant treatments	X	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Physical examination (height and body weight at Screening only)[j]	X[j]	X[j]														
Review contraception use	X	X[e]												X	X	X
Single supine 12-lead ECG	X		X[h]											X	X	
Single supine BP and PR	X		X[h]											X	X	
PF-06882961 administration			X													
PF-06865571 administration[k]			X[k]													
Standard meals/snacks[l]		X	X[h]					X			X					
Blood samples for:																
Safety laboratory tests	X	X												X	X	

Visit Identifier[a]	Screen Day -28 to -2	Periods 1 and 2[b]													ET/DC	F/U[c]
		Day -1	Day 1											Day 2		
Hours After Dose			0	0.5	1	2	3	4	6	8	10	12	16	24		
FSH[m]	X															
Serum pregnancy test[m]	X	X[e]														
HIV, HepBsAg, HCVAb, HCV RNA testing	X															
PF-06882961 PK			X[h]	X	X	X	X	X	X	X	X	X	X	X	X	
CCI			[redacted]													
Urine samples for:																
Urine drug screening	X	X[e,o]														
Urinalysis (and microscopy if needed)	X	X												X	X	

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

b. There will be a washout interval of at least 3 days between periods.

c. Follow-up contact may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.

d. Check potential COVID-19 exposure to positive subject, residence or travel in area of high incidence, and COVID-19 related signs and symptoms. Conduct approximately 24 hours before each visit and at least at each visit.

e. If participant is not discharged from the CRU between Periods 1 and 2, procedure only needs to be conducted in Period 1 only.

f. Testing for COVID-19 pathogen by PCR will be performed at each visit. For participants admitted for residence, a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4 x 24 hours in house if not discharged between periods), or if participant develops COVID-19 like symptoms.

g. To be done at least daily during residence.

h. Prior to dosing.

i. Discharge from CRU; participants may be confined to the CRU after completion of Day 2 activities in Period 1 at the discretion of the investigator.

j. Complete physical examination to be conducted upon admission of Period 1 only. Brief physical examinations may be performed as appropriate at other times at the investigator's discretion or if there are findings during the previous examination or new/open AEs. Height and weight to be measured at Screening only.

k. Only for the period with Treatment B.

l. While inpatient, meals to be provided at clock times matching nominal times of approximately 0H (breakfast), 4H (lunch), and 10H (dinner); snacks may be provided according to Section 5.3.1.

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

CCI [redacted]

o. A urine drug test is to be completed for both periods of this study unless participant is not discharged between periods. In additiona. *ad hoc* urine drug testing may be conducted throughout the study at the discretion of the investigator.

1.3.2. Schedule of Activities for Part B

Table 2. Part B – Overall Schedule of Activities

Visit Identifier	Screen	Period 1 (PF-06865571 Only)			Period 2 (PF-06882961 Only)				Period 3 (PF-06865571 plus PF-06882961)		Period 4 (PF-06865571 plus PF-06882961)			F/U Visit[a]	F/U Contact[a]	ET/DC
Day in Study Period[b]	**-28 to -2**	**-1**	**1**	**2**	**1**	**2**	**3-43**	**44**	**1**	**2**	**1-12**	**13**	**14**	**-**	**-**	**-**
Days in Study[c]	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5-45**	**46**	**47**	**48**	**49-60**	**61**	**62**	**68-71**	**89-96**	**-**
Informed consent & demography	X															
Outpatient visit (after ≥10 h fast)	X													X		
COVID-19 questionnaire[d]	X	X														
COVID-19 testing[e]	X	X				X[e]										
COVID-19 temperature check[f]	X	X	X	X	X	X	X[f]	X	X	X	X[f]	X	X	X		X
Inpatient stay at CRU		X	→	→	→	→	→	→	→	→	→	→	X[g]			
Eligibility criteria	X	X														
Medical and medication history	X	X														
C-SSRS and PHQ-9	X	X					X[h]				X[h]		X	X		X
Review drug, alcohol/tobacco use	X	X												X		
Review contraception use	X	X												X	X	X
Review prior or concomitant treatments	X	X	→	→	→	→	→	→	→	→	→	→	X	X	X	X
Serious and nonserious AE monitoring	X	X	→	→	→	→	→	→	→	→	→	→	X	X	X	X
Standardized meals/snacks[i]		X	→	→	→	→	→	→	→	→	→	→	X			
Physical exam (height at Screen only)[j]	X[j]	X[j]														
Body weight	X						X[h]				X[h]		X	X		X
Supine 12-lead ECG	X		X[k]				X[h]				X[h]		X	X		X
Supine BP and PR	X		X[k]				X[h]				X[h]		X	X		X
PF-06882961 administration[l]			Table 3		X	X	X	Table 3	Table 3	X	X	Table 3				
PF-06865571 administration[l]											X					
Blood samples for:																
Safety laboratory tests	X	X					X[h]				X[h]		X	X		X
Cystatin-C		X					X[h]				X[h]		X	X		X
PT/INR/aPTT	X	X					X[m]				X[m]		X	X		X
HIV, HepBsAg, HCVAb, HCV RNA testing	X															
FSH[n]	X															
Serum pregnancy test[n]	X	X					X[o]				X[o]					
TSH, lipids	X	X					X[m]				X[m]		X	X		X
Free T4, calcitonin, amylase, lipase, TBA	X	X					X[m]				X[m]		X	X		X

Visit Identifier	Screen	Period 1 (PF-06865571 Only)			Period 2 (PF-06882961 Only)				Period 3 (PF-06865571 plus PF-06882961)		Period 4 (PF-06865571 plus PF-06882961)			F/U Visit[a]	F/U Contact[a]	ET/DC
Day in Study Period[b]	**-28 to -2**	**-1**	**1**	**2**	**1**	**2**	**3-43**	**44**	**1**	**2**	**1-12**	**13**	**14**	**-**	**-**	**-**
Days in Study[c]	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5-45**	**46**	**47**	**48**	**49-60**	**61**	**62**	**68-71**	**89-96**	**-**
HbA1c	X															
PF-06882961 CCI PK																X
PF-06865571 PK				X[p]	X[q]					X[p]	X[q]					X
CCI		CC														
CP-I			X[s]				X[s]	X[s]								
4-β-hydroxycholesterol/cholesterol			X[t]				X[t]		X[t]							
Urine samples for:																
Urine drug screening[u]	X	X														
Urinalysis (& microscopy as appropriate)	X	X					X[h]				X[h]		X	X		X

a. The follow-up visit will occur 7-10 days after the final dose study intervention. The follow-up contact may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.

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

c. Day relative to first dose of study intervention on Day 1 of Period 1.

d. Check potential COVID-19 exposure to positive subject, residence or travel in area of high incidence, and COVID-19 related signs and symptoms. Conduct approximately 24 hours before and at least at each visit.

e. Testing for COVID-19 pathogen by PCR will be performed after 4 days (ie, upon completion of 4 x 24 hours in house), or if participant develops COVID-19 like symptoms.

f. To be done at least daily during residence.

g. Discharge from CRU.

h. Assessments to be performed on Days 8, 15, 22, 29, 36, 43, 50, and 57.

i. Meals to be provided at clock times matching nominal times of approximately 0H (breakfast), 4H (lunch), and 10H (dinner), with the exception Overall Study Day 46, Day 47, and Day 61 in which dinner will be provided at approximately 12H; snacks may be provided according to Section 5.3.1.

j. Complete physical examination to be conducted upon admission in Period 1. Brief physical examinations may be performed as appropriate at other times at the investigator's discretion or if there are findings during the previous exam or new/open AEs. Height to be measured at Screening only.

k. Prior to dosing.

l. Dosing to occur BID immediately after breakfast and dinner as specified in Section 5.3.1. Morning doses will be administered immediately after breakfast. On Overall Study Day 46, Day 47, and Day 61, evening doses will be administered immediately after dinner approximately 12 hours after morning dosing. On all other study days, evening doses will be administered immediately after dinner approximately 10 hours after morning dosing.

m. Assessments to be performed on Days 15, 29, 43, and 57.

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

o. Serum pregnancy test to be conducted on Day 30 and Day 60.

p. PK sample to be collected 24 hours after Day 1 and Day 47 morning doses of PF-06865571.

q. PK sample to be collected 48 hours after Day 1 and Day 47 morning doses of PF-06865571.

[redacted]

s. Samples to be collected at 0 (pre-dose), 12 and 24 hours after Day 1 morning dose of PF-06865571 and at 0 (pre-dose), 1, 2, 4, 6, 8 and 12 hours after Day 30 and Day 46 morning doses of PF-06882961.

t. Samples to be collected on Days 1, 19, 31, and 47 prior to morning dosing of study intervention(s).

u. A urine drug test is to be conducted at Screening. In addition, participants may undergo *ad hoc* urine drug screening throughout the study at the discretion of the investigator.

Table 3. Part B – Schedule of Activities for:

- **Day 1 of Period 1 (PF-06865571 ONLY) – Study Day 1.**
- **Day 44 of Period 2 (PF-06882961 ONLY) – Study Day 46.**
- **Day 1 of Period 3 (PF-06865571 plus PF-06882961) – Study Day 47.**
- **Day 13 of Period 4 (PF-06865571 plus PF-06882961) – Study Day 61.**

Hours Relative to Dosing at 0H	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**
PF-06882961 administration ***(Periods 2, 3, and 4 only)***	X[a]									X[b]		
PF-06865571 administration ***(Periods 1, 3, and 4 only)***	X[a]									X[b,c]		
Blood sampling for:												
PF-06882961 CCI PK ***(Periods 2 and 4 only; pre-dose in Period 3 only[d])***	X[d,e,f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[e,f]		
PF-06865571 PK ***(Periods 1, 3, and 4 only)***	X[e]	X	X	X	X	X	X	X	X	X[g]	X[h]	X[h]

a. Dosing to occur immediately after breakfast.

b. Dosing to occur immediately after dinner.

c. Period 4 only.

d. Only a predose sample will be collected on Day 1 of Period 3 (24 hours after morning dosing on Day 46 of Period 2; overall study Day 47). The full dense sampling scheme, including the predose sample, will occur in Periods 2 and 4.

e. Prior to dosing.

f. Serial PF-06882961 CCI PK samples to be collected in Periods 2 and 4 only.

g. The 12H PF-06865571 PK sample is to be collected in Periods 1, 3, and 4. In Period 4, the 12H sample is to be collected prior to administration of the evening dose of PF-06865571.

h. Periods 1 and 3 only.

2. INTRODUCTION

PF-06882961 is a potent, selective, orally bioavailable, small molecule agonist of the GLP-1 receptor and is presently in clinical development for the treatment of T2DM and obesity. PF-06865571 is a potent and selective inhibitor of DGAT2 being developed for the treatment of NASH with liver fibrosis. The current study will evaluate PK interactions following coadministration of PF-06882961 and PF-06865571 as a novel NCE:NCE combination because of the potential advantages offered by the combination over the individual investigational agents that could benefit a wider NASH population and/or target specific NASH sub-populations. The safety and tolerability of the investigational drugs administered together will also be assessed.

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 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] Administration of GLP-1 receptor agonists led to histological improvements in patients with NAFLD including resolution of NASH without worsening of fibrosis.[5]

DGATs catalyze the terminal step in TG synthesis; specifically, the esterification of a fatty acid with diacylglycerol resulting in the formation of TG.[6] In mammals, 2 structurally unrelated DGAT enzymes (DGAT1 and DGAT2) have been characterized. DGAT1 is highly expressed in the intestine and plays a central role in fat absorption.[7] DGAT2 is highly expressed in liver and adipose.[8] In preclinical models, blockade of hepatic DGAT2 using antisense oligonucleotides results in both down-regulation of the expression of multiple genes encoding proteins involved in lipogenesis and parallel induction in oxidative pathways.[9-11] The net result of these changes is a decrease in the levels of hepatic DAG and TG lipid which, in turn, reduces hepatocyte lipid burden and decreases hepatic very low density lipoprotein TG secretion.[9,11] Consistent with this, administration of DGAT2 inhibitors to patients with NAFLD reduces steatosis,[11,12] a necessary but not sufficient component of the pathogenesis of NASH.[13] PF-06865571 is postulated to decrease hepatic TG synthesis and hepatic lipid burden in NAFLD and NASH.

2.1. Study Rationale

The purpose of the study is to evaluate the PK interactions between PF-06882961 and PF-06865571 in healthy adult participants (Part A) and overweight adults or adults with obesity who are otherwise healthy (Part B).

2.2. Background

2.2.1. Non-Alcoholic Steatohepatitis

NASH is a clinical and histological subset of NAFLD (defined as presence of ≥5% hepatic steatosis) that is associated with increased all-cause mortality, cirrhosis and end-stage liver disease, increased cardiovascular mortality, and increased incidence of both liver related and nonliver related cancers.[14] Prevalence of NAFLD is estimated in North America to range from 27% to 34%, while prevalence of NASH in the general US population is estimated at

approximately 3-5%.[15] The 5-year (67%) and 10-year (38%) survival rates for patients with NASH are significantly different than for those with NAFLD.[16] The pooled liver-specific and overall mortality incidence rate estimates among those with NAFLD were calculated at 0.77 and 15.4, respectively, per 1000 person-years. In contrast, amongst the population with NASH, the incidence rate estimates were 11.8 (liver-specific) and 25.6 (overall) mortality.[17] During a follow-up of mean 20 years (range 0–40) equivalent to 139,163 person-years, 12% of NAFLD patients and 2.2% of controls developed severe liver disease (p=0.001).[18] Compared with controls, the risk of severe liver disease increased per stage of fibrosis. At the present time, treatment options are limited to management of associated conditions.[19] Although there are no therapies currently approved for the treatment of NASH, a growing body of evidence demonstrates the urgent medical need.[14]

NASH is a complex disease with a multifaceted pathogenesis, involving metabolic dysfunction, multiple inflammatory pathways, and fibrosis.[14] As a consequence, a single drug is unlikely to address all of the pathophysiologic components of NASH. Combining therapies that engage different biological targets and provide complementary benefits on the disease pathophysiology could provide greater efficacy and/or better tolerability to the patient and/or benefit for a larger fraction of the disease population than each individual monotherapy.

2.2.2. Nonclinical Pharmacokinetics

2.2.2.1. Nonclinical Pharmacokinetics and Metabolism of PF-06882961

Metabolism studies showed low turnover of PF-06882961 with some oxidative and glucuronide metabolites. All metabolites detected in human hepatocytes were also observed in hepatocytes from nonclinical species. PF-06882961 is expected to be cleared via hepatic uptake by OATP, followed by metabolic clearance principally mediated by CYP3A4/5, followed by CYP2C8 and CYP2C19. Non-CYP enzymes also contributed to the metabolism of PF-06882961.

PF-06882961 is a BCRP substrate. In addition, based on in vitro data, PF-06882961 has the potential to inhibit intestinal BCRP with an IC_{50} of 0.8 µM. Based on in vitro data, PF-06882961 demonstrated time-dependent inhibition of CYP3A4/5. The rate of inactivation was not saturated within the concentration ranges tested (5-150 µM), and therefore, the K_i and k_{inact} could not be calculated.

In vitro data also suggest a risk of PF-06882961 interaction with drugs for which CYP2C8 and UGT1A1 mediated metabolism constitutes the primary mechanism of clearance. At the dose of 200 mg BID, there is also a possibility of weak inhibition of hepatic OATP1B3, OATP2B1, OCT1 and uptake transporter MDR1. Static modeling of in vitro data also indicate that PF-06882961 has a low potential to cause DDIs as a result of induction of CYP3A4, or inhibition of other CYP enzymes (1A2, 2B6, 2C9, 2C19 or 2D6), other UGT enzymes (1A4, 1A6, 1A9, 2B7, 2B15), and uptake transporters OATP1B1, OCT2, MATE1, MATE2K, OAT1 and OAT3.

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

2.2.2.2. Nonclinical Pharmacokinetics and Metabolism of PF-06865571

In pivotal toxicity studies up to 16-weeks in rats and monkeys, systemic exposure of PF-06865571 increased with increasing dose, although in a less than dose proportional manner. In addition, PF-06865571 preferentially distributes into plasma versus red blood cells in vitro across the toxicology species and humans. In vitro screening suggests that PF-06865571 is a substrate for MDR1 (also known as P-gp) and mBcrp efflux transporters. The major primary metabolic pathway identified from preliminary in vitro and in vivo metabolite profiling in human is O-deethylation with subsequent sulfation and glucuronidation, with no evidence of human-unique metabolites. Reaction phenotyping studies indicate the total CYP contribution to PF-06865571 metabolism was >96% with CYP3A being the predominant isoform. Modeling suggests a moderate risk of clinical DDI with PF-06865571 as a victim upon coadministration with CYP3A4 inhibitors or inducers.

Assessment of the DDI potential for PF-06865571 was based on the mean steady-state unbound C_{max} of 2.07 µM for PF-06865571 following oral administration at the highest planned clinical dose of 600 mg/day (300 mg BID). PF-06865571 mediated DDIs associated with inhibition of CYP and UGT enzymes are not expected, with the exception of CYP2C9, intestinal CYP3A4/5, UGT1A1, UGT1A9, and UGT2B15. In human hepatocytes, PF-06865571 induces CYP2B6 and CYP3A4 (enzymatic and mRNA) but not CYP1A2. In vitro evaluations indicated that PF-06865571 has a low potential to inhibit OAT1, OAT3, MATE2K, OATP1B1, and OATP1B3 transporters at clinically relevant concentrations; however, PF-06865571 does have the potential to inhibit P-gp, BCRP, OCT1, OCT2, and MATE1.

Refer to the IB for more details on the nonclinical PK and metabolism of PF-06865571.

2.2.3. Nonclinical Toxicology

2.2.3.1. Summary of Toxicology Studies with PF-06882961

PF-06882961 was administered to Wistar-Han rats and cynomolgus monkeys in oral studies up to 6 months in duration. In addition, PF-06882961 was evaluated in genetic toxicity studies, dose-range-finding and definitive EFD studies in rats and rabbits, fertility and early embryonic study in rats, and in vitro and in vivo phototoxicity studies. PF-06882961 was not genotoxic or phototoxic.

Based on the nonclinical toxicity studies conducted, effects were observed in the cardiovascular and gastrointestinal systems, liver, thyroid, and Harderian gland. The NOAELs in the 6-month toxicity study in rats and 14-week toxicity study in monkeys with a 4-week lead-in (ie, the longest duration nonclinical studies supporting this clinical trial) were associated with systemic exposures (based on AUC_{24}) which are approximately 23x (for rat) and 1.2x (for monkey) higher than the clinical exposures anticipated at the highest planned dose of 200 mg BID in C3421038. The NOAEL in the 14-week plus 4-week lead-in monkey toxicity study was based on decreases in food consumption and body weight at a higher dose, which are considered monitorable and reversible. Please refer to Section 5.3.3 of the IB for details.

2.2.3.2. Summary of Toxicology Studies with PF-06865571

In GLP-compliant studies, PF-06865571 was administered to rats in toxicity studies up to 6 months in duration. In the pivotal chronic 6-month toxicity study with 1-month (4-week) recovery, there were no adverse effects and no unique findings that were not evident in previous toxicity studies. All test article-related effects were reversed at the end of the recovery phase. The NOAEL was 1000 (500 BID) mg/kg/day, the highest dose tested, based on the absence of any adverse effects.

PF-06865571 was administered to cynomolgus monkeys in GLP-compliant pivotal toxicity studies up to 9-months in duration. In the pivotal 9-month chronic toxicity study with a 1-month recovery, PF-06865571 was tolerated at all doses with no adverse or nonadverse findings. Therefore, 1000 (500 BID) mg/kg/day, the highest dose tested, was the NOAEL. Additional details of nonclinical studies are provided in PF-06865571 IB Section 5.3, and an overview of the toxicity testing program is included in Table 5.3-1 of the PF-06865571 IB.

2.2.3.3. Summary of Toxicology Study for Co-administration of PF-06882961 and PF-06865571

In the completed 2-week oral gavage toxicity study of the co-administration of PF-06882961 and PF-06865571 in Wistar Han rats, PF-06882961 was administered once daily at 75 mg/kg/day, and PF-06865571 was coadministered twice daily at 1000 (500 BID) mg/kg/day by oral gavage for 2 weeks with no adverse test-article related effects observed. Non-adverse test article-related effects were limited to higher liver weights in both sexes, minimal centrilobular hepatocellular hypertrophy in a female, lower T3, T4, and cholesterol in both sexes, lower triglycerides in males, and lower glucose in females. This coadministration was considered the NOAEL and was associated with a C_{max} of 5210 ng/mL and 18,500 ng/mL and AUC_{24} of 19,300 ng•h/mL and 69,000 ng•h/mL on Day 14 in males and females, respectively, for PF-06882961. The corresponding PF-06865571 C_{max} of 14,000 ng/mL and 29,400 ng/mL and AUC_{24} of 185,000 ng•h/mL and 427,000 ng•h/mL was obtained on Day 14 in males and females, respectively.

2.2.4. Clinical Overview

2.2.4.1. Summary of Clinical Safety

2.2.4.1.1. Clinical and Safety Experience with PF-06882961

Three clinical studies have been completed with PF-06882961 in which 135 participants were dosed, and 110 participants were exposed to single or multiple doses of PF-06882961 (Table 6-1 in the PF-06882961 IB). In addition, ongoing studies include a 16-week Phase 2 dose ranging study in T2DM (C3421005), a multiple dose PK/PD study in Japanese participants with T2DM (C3421015), a single dose ADME and oral bioavailability study (C3421009), and a single dose formulation comparison study in healthy participants (C3421010). Two studies, C3421001 and C3421003, were completed in healthy participants (total of 37 healthy participants randomized), and 1 study, C3421002, was completed in participants with T2DM (total of 98 T2DM participants randomized). In these studies, PF-06882961 was found to be generally safe and well tolerated. In C3421001, 25 healthy participants were randomized to single ascending oral doses of PF-06882961 or placebo. In

C3421003, 12 healthy participants were randomized to receive single doses of different oral formulations of PF-06882961. In C3421002, 98 participants with T2DM were randomized to multiple ascending oral doses of PF-06882961 or placebo for 28 days. In this study PF-06882961 doses ranging from 10 mg BID to 120 mg BID were studied. A total of 98 participants with T2DM on a background anti-diabetic regimen of metformin were randomized to receive PF-06882961 or matching placebo in a 3:1 randomization ratio, and 92 participants completed the study. Six participants discontinued from the study, of which 2 discontinuations were due to treatment-related TEAEs and 4 withdrew during the treatment or follow-up period for non-treatment related reasons. A total of 319 TEAEs were reported, of which the majority of the AEs [294 (92%)] were mild in severity, 23 (7%) were moderate, and 2 (1%) were severe in intensity. The most frequently reported TEAEs were nausea (49.0%), dyspepsia (32.7%), vomiting (26.5%), diarrhea (24.5%), headache (23.5%), and constipation (20.4%). One participant experienced a mild TEAE of hypoglycemia. This AE was non fasting, mild in severity and of limited duration. There were no deaths and no treatment-related SAEs with repeated dosing of PF-06882961 in patients with T2DM. Overall, the doses of PF-06882961 studied in C3421002 were safe and well tolerated.

Preliminary clinical and safety data are available from the C3421007 Phase 1 study, which assessed the effect of PF-06882961 on the pharmacokinetics of rosuvastatin and midazolam. In this study, PF-06882961 doses up to 200 mg BID were administered with 4-day titration steps in 16 otherwise healthy, adult participants with obesity. Of these participants, 14 completed the 17-week study duration, and 2 participants discontinued for reasons not related to AEs. A total of 129 TEAEs have been reported to date, of which the majority of the AEs (127/129) were mild in severity and 2 were moderate. There was 1 mild TEAE of increased transminitis (also reported as an SAE), which occurred at the end of the dosing duration, after co-administration of PF-06882961 200 mg BID with rosuvastatin 10 mg once and midazolam 2 mg once, administered seperately in successive periods. The transaminase levels returned to baseline levels in the follow up period. No significant elevations were noted in total bilirubin, alkaline phosphatase or GGT. The most frequently reported all causality TEAEs in the study participants have been nausea (26), constipation (12), decreased GFR (12), headache (10), and vomiting (9). 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. Mild declines from baseline were noted in GFR, with most values remaining above 70 mL/min, and occurred in the setting of weight loss, which was expected with the mechanism of action. Most GFR levels returned to pre-dose levels by follow-up.

2.2.4.1.2. Clinical and Safety Experience with PF-06865571

Eight clinical studies with PF-06865571 have been completed (Table 6-1 in the PF-06865571 IB). In addition, ongoing studies include a 6-week Phase 2a study evaluating PF-06865571 in combination with an ACC inhibitor in participants with NASH (C3711005), a 48-week Phase 2b dose ranging study evaluating PF-06865571 alone and in combination with an ACC inhibitor in participants with NASH (C2541013), and a single dose ADME study in healthy participants (C2541007). Across the 8 completed studies, a total of 280 unique participants have been randomized. This includes 132 unique healthy adult participants and 148 adults

with NAFLD. Overall, 38 unique participants (14%) have been exposed to a single, oral dose of PF-06865571 only; and an additional 167 participants (60%) have received repeated doses of PF-06865571. In the clinical program, following single oral doses of PF-06865571, across the 300-fold dose range evaluated (ie, 5 mg to 1500 mg), the all causality, TEAEs reported in ≥4 participants were headache (12%) and diarrhea (7%). Upon repeated administration of PF-06865571, across the 20-fold dose range evaluated (ie, 90 to 1800 mg/day), TEAEs reported in ≥7 participants across all arms evaluated were headache (11%), diarrhea (6%), fatigue (5%), pruritus (4%), abdominal pain (3%), and nausea (3%). Across 5 clinical studies completed with repeated dosing of PF-06865571, 5 SAEs have been reported, 4 of them post-randomization. These include 2 deaths, both considered unrelated to study drug (Table 6.2-4 in PF-06865571 IB). In the clinical experience to date, MTD has not been identified and with administration of PF-06865571 alone, there have been no identified adverse drug reactions.

2.2.4.2. Summary of Clinical Pharmacology and Biopharmaceutic Studies

2.2.4.2.1. Clinical Pharmacokinetics of PF-06882961

The clinical PK of PF-06882961 in adult participants has been evaluated in 3 completed studies: C3421001, C3421002, and C3421003. The results of these completed studies are summarized in the PF-06882961 IB, Section 6.1.

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

In study C3421002, following 28 days of dosing to participants with T2DM, accumulation was modest for the BID IR formulation treatments, with mean ratios based on dose-normalized AUC_{24} (R_{ac}) values ranging from 1.203 to 2.009. Day 28 plasma exposure as measured by geometric mean AUC_{24} values appeared to increase in an approximate dose proportional manner across all IR treatments. Mean $t_{½}$ values on Day 28 across all treatments ranged between 4.681 to 8.090 hours, and no apparent trends were observed across various treatments, regimens, or doses administered. Interparticipant variability for PF-06882961 exposure was based on geometric mean was 31%-87% for AUC_{24} and 32%-94% for C_{max} and on Day 28 across all treatments and cohorts. A population PK model based on data from C3421001 and C3421002 indicated that the exposure in T2DM participants (C3421002) was approximately 1.7-fold higher than that observed in healthy participants (C3421001) after accounting for differences in body weight between the participants in each study.

CCI

Preliminary draft data from Study C3421007 indicate that PF-06882961 has the potential to interact with drugs metabolized by CYP3A, as observed via co-administration with the sensitive probe CYP3A substrate, midazolam. When co-administered with 120 mg BID PF-06882961, midazolam C_{max} and AUC_{last} decreased by approximately 37% and 49%, respectively. When co-administered with 200 mg BID PF-06882961, midazolam C_{max} and AUC_{last} decreased by approximately 28% and 45%, respectively.

Additionally, preliminary draft data from this study indicate a potential interaction between PF-06682961 and substrates of BCRP, as observed via co-administration with the sensitive probe BCRP substrate, rosuvastatin. When co-administered with 120 mg BID PF-06882961, rosuvastatin C_{max} and AUC_{last} increased approximately 2.6-fold and 2.1-fold, respectively. When co-administered with 200 mg BID PF-06882961, rosuvastatin C_{max} and AUC_{last} increased approximately 4.5-fold and 2.9-fold, respectively.

2.2.4.2.2. Clinical Pharmacokinetics of PF-06865571

Upon repeated dosing of PF-06865571 with standard meals, C_{max} was achieved at 1.5 to 3 hours post dose. Steady-state plasma concentrations were achieved by Day 4, and the mean terminal $t_{½}$ ranged from 3.3-6.9 hours. Given the short mean terminal $t_{½}$ accumulation is likely to be negligible at a dosing frequency of Q12H/BID as minimal accumulation was observed upon repeated dosing at a frequency of Q8H. Dosing in the fasted state resulted in lower exposures (ie, AUC_{inf} 39% lower and C_{max} 34% lower than when a 1000 mg dose of PF-06865571 was administered with a standard meal). Across the range of repeated doses evaluated (90 mg/day to 1800 mg/day, administered Q8H), the plasma exposure increased in a dose proportional manner. Less than 2% of the PF-06865571 dose administered was excreted unchanged in the urine indicating that renal clearance is not a major clearance mechanism for PF-06865571. PF-06865571, dosed at 300 mg BID, was shown to increase metformin (500 mg single dose) exposure (ie, both AUC_{inf} and C_{max}) by approximately 2-fold.

2.3. Benefit/Risk Assessment

PF-06882961 and PF-06865571 are not expected to provide any clinical benefit to participants in this study. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06882961 and PF-06865571 may be found in the IB for PF-06882961 and separately for PF-06865571, which are the SRSDs for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention – PF-06882961 (GLP-1 receptor agonist)		
Thyroid C-cell tumors	The potential risks are based on product labeling for injectable GLP-1 receptor 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 multiple endocrine neoplasia syndrome type 2 (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-1 receptor 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-1 receptor 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 T2DM would not be taking anti-diabetic agents and therefore would not be expected to have an increased risk for hypoglycemia. Only one AE 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 AE (Preferred Term: blood creatinine increased) has been observed.	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 BUN, creatinine, and eGFR.
Gastrointestinal adverse reactions	The potential risks are based on product labeling for injectable GLP-1 receptor agonists (ie, liraglutide, exenatide and dulaglutide). In addition, gastrointestinal AEs, the majority of which were mild in severity, have been observed in the clinical program with PF-06882961. In nonclinical studies with PF-06882961, gastrointestinal AEs have been observed 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 200 mg BID over 44 days in this study. Exclusion criteria include any factor that may affect drug absorption, such as bariatric surgery, active inflammatory bowel disease or an intestinal resection.
Diabetic retinopathy complications	The potential risk is based on the product labeling for the injectable GLP-1 receptor agonist semaglutide for T2DM. This risk has not been listed in the prescribing information for other marketed GLP-1 receptor agonists. There are no nonclinical or clinical data involving PF-06882961 to suggest an increased risk of diabetic retinopathy complications.	Study excludes participants with T1DM or T2DM or secondary forms of diabetes.
Suicidal ideation and behavior	The potential risk is based on the product labeling for the injectable GLP-1 receptor agonist liraglutide for obesity. This risk has not been listed in the prescribing information for other marketed GLP-1 receptor agonists for T2DM. 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 HR have been reported for marketed GLP-1 receptor agonists (eg, liraglutide), and increases in HR have been observed with PF-06882961 administration, with most HR values within the normal range. There have been incidences of HR >120 bpm in the clinical program to date and no AEs related to elevations in HR. In addition, declines in systolic BP have been noted at higher doses of PF-06882961.	BP, PR, and ECGs will be monitored at frequent intervals during the clinical study.
Declines in body weight	Decreased appetite and body weight loss have been reported for marketed GLP-1 receptor 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-1 receptor 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 – PF-06865571 (DGAT2 inhibitor)		
Food effect resulting in change in PF-06865571 exposure	PF-06865571 exposures are lower in fasted state than in fed state.	Study interventions will be taken with a meal.
Fetal skeletal variations as a result of transient developmental delay	In an embryo-fetal development toxicity study in rats, lower fetal body weight and skeletal anomalies observed at all doses with NOAEL for this developmental toxicity not identified. In an embryo-fetal development toxicity study in rabbits, no developmental toxicity observed.	• Communicated through Section 7 of the PF-06865571 IB (Jan-2020). • Enrollment of WOCBP restricted to those using effective contraception. • In males who are sexually active with a female partner of childbearing potential, use of barrier methods not required/mandated given safety margins ≥100-fold.

Other		
Risk of COVID-19 infection for participants	During the pandemic, healthy participants could be infected with the SARS-COV-2 virus through study participation. This could lead to increased health risk for participants and others in the study and could lead to confounding AE with study intervention.	COVID-19 specific assessments according to SoA.

2.3.2. Benefit Assessment

While PF-06882961 and PF-06865571 are not expected to provide any clinical benefit to otherwise healthy adult participants with obesity in this study, potential benefits for participants in this study may include receiving medical evaluations/assessments associated with clinical study visits (eg, physical examinations, ECGs, clinical safety laboratory assessments), and contributing to the process of developing a potential new therapy for NASH with liver fibrosis.

2.3.3. Overall Benefit/Risk Conclusion

In consideration of the available clinical and nonclinical data, and the measures taken to minimize risk to participants in this study, the overall benefit/risk profile supports clinical testing of the combination of PF-06882961 and PF-06865571.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part A	
Primary:	**Primary:**
• To evaluate the effects of PF-06865571 on the single-dose pharmacokinetics of PF-06882961 in healthy adult participants.	• PF-06882961 plasma pharmacokinetic parameters: C_{max} and AUC_{24}.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-06882961 alone and in combination with PF-06886571 when administered to healthy adult participants.	• Assessment of treatment-emergent adverse events, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters during the entire study.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To evaluate the effects of PF-06865571 on additional pharmacokinetic parameters of PF-06882961 in healthy adult participants.	• Additional PF-06882961 plasma pharmacokinetic parameters: T_{max}.
Part B	
Primary:	**Primary:**
• To evaluate the effects of PF-06882961 on the single-dose pharmacokinetics of PF-06865571 in overweight adults or adults with obesity who are otherwise healthy. • To evaluate the effects of PF-06865571 on the multiple-dose pharmacokinetics of PF-06882961 in overweight adults or adults with obesity who are otherwise healthy.	• PF-06865571 plasma pharmacokinetic parameters on Day 1 and Day 47: C_{max}, AUC_{last}, and $AUC_{inf,}$ as data permits. • PF-06882961 plasma pharmacokinetic parameters on Day 46 and Day 61: C_{max} and AUC_{12}.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-06882961 and PF-06865571 when administered separately and in combination in overweight adults or adults with obesity who are otherwise healthy.	• Assessment of treatment-emergent adverse events, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters during the entire study. • Assessment of mental health as determined by C-SSRS and PHQ-9 in Part B of the study.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To evaluate the effects of PF-06882961 on additional pharmacokinetic parameters of PF-06865571 in overweight adults or adults with obesity who are otherwise healthy. • To evaluate the effects of PF-06865571 on additional pharmacokinetic parameters of PF-06882961 in overweight adults or adults with obesity who are otherwise healthy.	• Additional PF-06865571 plasma pharmacokinetic parameters on Day 1 and Day 47: T_{max}, CL/F, V_z/F, and $t_{½}$, as data permits. • Additional PF-06882961 plasma pharmacokinetic parameters on Day 46 and Day 61: T_{max} and CL/F.
CCI	
• To evaluate the effects of PF-06882961 on the multiple-dose pharmacokinetics of PF-06865571 in overweight adults or adults with obesity who are otherwise healthy.	• PF-06865571 plasma pharmacokinetic parameters on Day 61: C_{max}, T_{max}, and AUC_{12}.

• To evaluate the effects of multiple doses of PF-06882961 on CYP3A induction in overweight adults or adults with obesity who are otherwise healthy. • To evaluate the effect of multiple doses of PF-06882961 on coproporphyrins I in overweight adults or adults with obesity who are otherwise healthy.	• Morning pre-dose 4-β-hydroxycholesterol/cholesterol plasma ratio on Days 1, 19, 31, and 47. • CP-I parameters on Days 30 and 46: AUC_{12} and C_{max}.

4. STUDY DESIGN

4.1. Overall Design

This study will be conducted in 2 parts. Part A will evaluate the effect of PF-06865571 on the PK of PF-06882961. Part B will evaluate the effect of PF-06882961 on the PK of PF-06865571, as well as the effect of PF-06865571 on the PK of PF-06882961.

4.1.1. Part A Study Design

Part A of this study is an open-label, two-period, two-sequence, crossover study to investigate the potential effect of PF-06865571 on the single-dose PK of PF-06882961 in a cohort of approximately 8 participants who complete both treatment periods. The sequences are planned to be executed in parallel.

All doses of PF-06882961 and PF-06865571 will be administered with meals.

All participants will provide informed consent and undergo screening evaluations to determine their eligibility. Screening will occur within 28 days prior to administration of the study intervention for each participant on Day 1. Participants will be admitted to the CRU on Day -1. Each participant is planned to undergo two treatment periods, in a randomized order, as outlined in Section 1.2.1, with a washout interval between periods of at least 3 days following the final dose of study intervention administered in Period 1.

Participants will be discharged from the study on Day 2 of period 2. Between periods, participants may be discharged after Day 2 of Period 1 or be confined to the CRU until the completion of Day 2 activities of Period 2 at the discretion of the investigator. A follow-up contact will occur 28-35 days after the final dose of study intervention. For individual participants, the total duration of participation from the screening visit to the follow-up contact will be approximately 9 weeks.

Participants who withdraw from Part A of the study for non-safety-related reasons, or who are unable to complete both treatment periods in the study, may be replaced at the discretion of the sponsor upon consultation with the investigator.

4.1.2. Part B Study Design

Part B of this study will be conducted as an open-label, fixed-sequence study to evaluate the effect of PF-06882961 on the single-dose PK of PF-06865571, as well as the effect of PF-06865571 on the multiple-dose PK of PF-06882961 in overweight adults or adults with obesity who are otherwise healthy.

In Period 1, a single oral dose of PF-06865571 will be administered. Following titration of PF-06882961 to a maximal steady-state dose to be determined as described in Section 4.3 (Period 2), the effect of steady-state administration of PF-06882961 on a single oral dose of PF-06865571 will be assessed (Period 3). Following Period 3, multiple doses of PF-06865571 will be administered with a maximally tolerated dose of PF-06882961 to be determined as described in Section 4.3 (Period 4) to assess the effect of steady-state doses of PF-06865571 on multiple dose PK of PF-06882961. The titration scheme is outlined in Section 6.1.1 and Section 6.3.1.

Approximately 16 participants will be enrolled such that approximately 12 evaluable participants complete Part B. The study schema is outlined in Section 1.2.2.

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 CRU on Day -1 of Period 1. The total duration of participation from Screening to the follow-up contact will be approximately 18 weeks. The follow-up visit will occur 7-10 days after the final dose of study intervention. The follow-up contact may occur via telephone contact and will occur 28-35 days after the final dose study intervention. Participants who withdraw from Part B of the study for non-safety-related reasons 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-06865571 on the PK of PF-06882961, as well as the effect of PF-06882961 on the PK of PF-06865571. Based on in vitro studies, PF-06882961 has a low risk of time-dependent inhibition of CYP3A4. PF-06865571 has modest risk of induction of CYP3A. Both PF-06882961 and PF-06865571 are CYP3A substrates with f_m values of 0.50 and 0.68, respectively.

In addition, PF-06865571 is also an inhibitor of P-gp and BCRP, and PF-06882961 is a BCRP substrate in vitro. Therefore, in order to address the potential for increased exposure of PF-06882961 caused by a potential interaction with PF-06865571, the effect of PF-06865571 on the PK of PF-06882961 will first be evaluated in Part A followed by a pause to evaluate the PK results and inform doses for Part B. Healthy adult participants will be enrolled in Part A.

Part A of the study is not a definitive assessment of the effect of PF-06865571 on the PK of PF-06882961 because the duration of dosing of PF-06865571 is not adequate to assess potential inductive effects. However, because Part B is to be conducted at the highest tolerated dose of PF-06882961, and PF-06865571 has the potential to increase PF-06882961 concentrations via inhibition of BCRP, Part A is being conducted in advance of Part B to mitigate potential for PF-06882961 exposures in this study beyond what was previously assessed in prior clinical experience.

In Part B, multiple dosing will be used to ensure maximal clinically relevant steady-state PF-06882961 exposures are achieved in order to more fully evaluate potential CYP3A time-dependent inhibition by PF-06882961 and potential CYP3A induction by PF-06865571.

Based on in vitro data, the risk of time-dependent inhibition of CYP3A by PF-06882961 is low, so increases in PF-06865571 exposures are not expected. In fact, the preliminary data from the C3421007 DDI study indicate that PF-06882961 co-administration decreased the exposure of midazolam, a probe 3A4 substrate. To investigate the mechanism of this interaction, plasma 4-β-hydroxycholesterol/cholesterol, used as an endogenous probe for CYP3A induction, will be collected and analyzed in this study.

At the PF-06882961 200 mg BID dose, there is a possibility of weak inhibition of the hepatic uptake transporters OATP1B3 and OATP2B1. CP-I has been reported to be used as an endogenous probe for OATP1B activities. In the clinical DDI study of rosuvastatin and rifampicin, CP-I exposure (AUC_{24}) was increased by 4.0-fold with co-administration of rifampicin, a potent OATP1B1 inhibitor, compared to the group of rosuvastatin alone.[28] Therefore, CP-I will be assessed in Part B to evaluate the potential effect of PF-06882961 on OATP1B at higher doses (ie, 120 and 200 mg BID). This data could help understand the contribution of OATP1B inhibition to the rosuvastatin exposure increase observed in the C3421007 study where rosuvastatin was co-administered with PF-06882961. In the study mentioned above, it was also suggested that CP-I plasma concentration at baseline were constant and independent of time, but changed rapidly following co-administration with rifampicin and returned back to baseline within 24 hours.[28] Therefore, three blood samples will be taken at different timepoints prior to PF-06882961 treatment in Part B to determine baseline CP-I concentrations followed by CP-I concentration time profiles over 12 hours for both PF-06882961 120 mg and 200 mg BID at steady-state, respectively.

Participants with a higher BMI range from 25 kg/m^2 to 40 kg/m^2 who are overweight or obese but otherwise healthy will be enrolled in Part B to target a similar BMI range as patients with NASH. Adult participants with NASH often have co-existing obesity, and PF-06882961 will likely be co-administered with PF-06865571 in a future clinical efficacy study.

The elimination half-lives of PF-06882961 and PF-06865571 are approximately ≤8 hours and ≤7 hours, respectively, following single and multiple dosing. Therefore, plasma sampling will be collected for 24 hours after dosing in Part A and for 12 to 48 hours after dosing in Part B.

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Clinical laboratory tests, assessments of vital signs, body weight, 12-lead ECGs, physical examinations, and AE monitoring will provide data to evaluate the safety and tolerability of PF-06882961 and PF-06865571 when dosed alone and in combination. 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. Body weight will be measured at timepoints in the SoA because GLP-1 receptor agonists have been shown to decrease food intake and body weight.

As part of the clinical safety laboratory tests, fasting blood glucose will be used to assess changes in glycemic parameters. In addition, calcitonin, amylase, and lipase will be assessed, as these laboratory parameters have been shown to increase with marketed GLP-1 receptor agonists.[20-23] In addition, TSH, free T4, lipids, coagulation profile, and TBA will also be assessed based on non-adverse findings in the nonclinical studies with PF-06882961. Furthermore, PF-06865571 is a dose-dependent inhibitor of the transporters OCT2/MATE in the kidney and, as expected, this has been observed to cause increases in serum creatinine in previous clinical studies with PF-06865571 without a change in renal function, as assessed via measurements of Cystatin-C. Therefore, Cystatin-C (and eGFR using CKD-EPI-Cystatin-C) will be measured in Part B to accurately monitor renal function starting at baseline and throughout the study. Assessment of suicidal ideation and behavior will be conducted using C-SSRS,[24] and PHQ-9[25] will also be performed based on the potential risk related to the product labeling for the injectable GLP-1 receptor agonist liraglutide[23] in patients with BMI ≥30 kg/m^2.

While GLP-1 receptor 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 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 both PF-06882961 and PF-06865571 is planned to occur in the fed state, immediately after standard breakfast and dinner, because this is the anticipated mode of administration in clinical use.

Human reproductive safety data are not currently available for co-administration of PF-06882961 and PF-06865571. Marketed GLP-1 receptor agonists are listed as contraindicated in pregnancy.

Embryo-fetal developmental studies with PF-06882961 alone and PF-06865571 alone have been completed, and findings have been noted (refer to Section 2.3.1). The use of a highly effective method of contraception is required by females of childbearing potential who are enrolled in this study. Refer to Section 5.3.4, Section 6.5, and Appendix 4 for additional details.

The potential risk of exposure to PF-06882961 and/or PF-06865571 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.[26]

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4.3. Justification for Dose

4.3.1. PF-06882961

4.3.1.1. PF-06882961 in Part A

A single oral dose of 20 mg of PF-06882961 will be used in Part A. Doses up to 120 mg were previously administered in the Phase 1 C3421002 study and were sufficiently well tolerated. Because only modest exposure increases of PF-06882961 are anticipated in this study, a 20 mg dose of PF-06882961 is anticipated to be safe and generally well tolerated in healthy adult participants even if a potential PK drug-drug interaction increases the exposure of PF-06882961.

4.3.1.2. PF-06882961 in Part B

The highest planned steady-state dose in the Phase 2 obesity POC study is 200 mg BID (C3421019). Similarly, 200 mg BID is the highest planned steady-state dose in a drug interaction study (C3421007) investigating the effect of PF-06882961 on the PK of midazolam (3A4 substrate) and rosuvastatin (BCRP substrate). Based on a population PK analysis of Phase 1 data including both T2DM and non-T2DM participants, the exposure in T2DM participants are projected to be 1.7-fold higher than non-T2DM. Based on this analysis, the exposure in participants with obesity in these studies are expected to be comparable to the exposure of 120 mg BID in T2DM, which was generally well tolerated in the multiple ascending dose study C3421002. However, no clinical data are available (at the time of finalization of this protocol) evaluating doses >120 mg BID in any participant population.

Preliminary safety and tolerability data from C3421007 will be reviewed prior to final dose and titration scheme selection for this study. If 200 mg BID is well tolerated in C3421007, then a steady-state dose of 200 mg BID will be used in this study. If 200 mg BID is not well tolerated in C3421007, then a lower steady-state dose will be selected for this study.

Accordingly, the maximal practical and well tolerated dose of PF-06882961 is envisioned for use in this study. This is consistent with expectation that the PF-06882961 dose needed for treatment of NASH is similar to that required for maximal efficacy in obesity.

The titration to PF-06882961 200 mg BID is planned over approximately 44 days but may also be revised based on C3421007 study results. Part B doses of PF-06882961 may be reduced if PF-06865571 increases PF-06882961 AUC_{24} by >50% in Part A.

The titration scheme is outlined in Section 6.1.1 and Section 6.3.1.

4.3.2. PF-06865571 in Part A and Part B

300 mg doses of PF-06865571 will be administered in both parts of this study. PF-06865571 doses at 300 mg BID are expected to have an acceptable safety and tolerability profile, with minimal risk to the participants of study, because oral doses of PF-06865571 as high as 600 mg Q8H have demonstrated an acceptable safety and tolerability profile after 14 days of oral administration. Given the short $t_{½}$, PF-06865571 is anticipated to have minimal steady-state accumulation. The 300 mg BID dose of PF-06865571 administered in this study represents the highest dose being assessed in the Phase 2 study in participants with biopsy-proven NASH with fibrosis. Doses achieving exposures greater than 300 mg BID were also administered in the Phase 1 C2541002 study and will therefore allow DDI assessment in this study at anticipated exposures that were sufficiently tolerated.

A positive food effect has been observed in previous clinical studies with PF-06865571. Therefore, to maximize exposures, and to dose PF-06865571 similarly to how it will be dosed in future studies, PF-06865571 will be administered with food.

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, approximately 28 to 35 days after the 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. Male and female participants who are overtly healthy (other than being overweight or obese in Part B only) as determined by medical evaluation including medical history, physical examination, and laboratory tests.

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

Weight:

4. BMI and total body weight:

    - Part A: BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb);

    - Part B: BMI ≥25 kg/m^2 and not more than 40 kg/m^2 at Screening; 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, gastrectomy, cholecystectomy, bariatric surgery, active inflammatory bowel disease, or an intestinal resection).

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-1 receptor agonists.

5. Known intolerance or hypersensitivity to DGAT2 inhibitors.

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 or multiple endocrine neoplasia syndrome type 2, or study participants with suspected medullary thyroid carcinoma 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. See Section 6.5 for prohibited prior/concomitant medications.

Prior/Concurrent Clinical Study Experience:

19. 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). An emergency use authorized or approved COVID-19 vaccine is considered a concomitant medication.

20. Known prior participation in a clinical trial with PF-06882961 or PF-06865571.

Diagnostic Assessments:

21. Part B only: A Patient Health Questionnaire (PHQ-9) score ≥15 obtained at Screening or Day -1.

22. Part B only: Response of "yes" to question 4 or 5, or on any behavioral question on the C-SSRS at Screening or Day -1.

23. A positive urine drug test.

24. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

25. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTc 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 the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc 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.

26. A positive COVID-19 test at or after screening.

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%.
    - AST **or** ALT > ULN.
    - Total bilirubin level > ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and are eligible for this study provided the direct bilirubin level is ≤ ULN.
    - TSH > ULN or < LLN.
    - Serum calcitonin > ULN.
    - Amylase or lipase > ULN.
    - Fasting blood glucose ≥126 mg/dL.
    - Fasting triglycerides >200 mg/dL.
    - INR > ULN.
    - PLT < LLN.
    - eGFR <80 mL/min/1.73 m^2 as calculated by the 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.

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 dose 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 evaluations and the morning predose PK evaluations.

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

- Participants should begin consumption of a standard breakfast (morning) and dinner (evening) approximately 30 minutes prior to dosing. The breakfast and dinner will be consumed over approximately a 20 minute period, with the study intervention administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to complete the entire meal. Study intervention will be administered as outlined in Section 6.1.1.

- Noncaffeinated drinks (except red wine, grapefruit or grapefruit-related citrus fruit juices; see below) may be consumed with meals and the evening snack. Caffeine containing drinks may be consumed during the study but not within 1 hour prior to measuring vital signs and ECGs (see Section 5.3.2).

- Lunch will be provided approximately 4 hours after morning dosing.

- On Overall Study Day 46, Day 47, and Day 61 in Part B, dinner will be provided approximately 12 hours after morning dosing. On all other study days in both Part A and Part B, dinner will be provided approximately 10 hours after morning dosing.

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

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

5.3.2. Caffeine, Alcohol, and Tobacco

- Tobacco or nicotine use may be allowed according to CRU practices but not in excess of the equivalent of 5 cigarettes per day as outlined in Section 5.2.

- 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.

- 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 CRU and continue abstaining from alcohol until collection of the final PK sample of the study. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

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, eating, and drinking beverages other than water during the first 4 hours after morning dosing on days of post-dose PK sample collections (except when required for BP, PR, 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 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled 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 due to unexpected delays (eg, delayed drug shipment), will not be required to rescreen if the laboratory results obtained prior to first dose administration meet eligibility criteria.

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

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to PF-06882961 and PF-06865571.

6.1. Study Intervention(s) Administered

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

PF-06865571 tablets (100 mg) will be supplied by Pfizer to the CRU in bulk along with individual dosing containers, as necessary, for unit dosing.

6.1.1. Administration

All PF-06882961 and PF-06865571 doses will be administered with food in both Part A and Part B as described in Section 5.3.1.

In Part A, participants will receive study intervention as applicable per SoA. Doses will be administered with breakfast at approximately 0800 hours (plus or minus 2 hours).

In Part B, participants will receive PF-06882961 and PF-06865571 as applicable per SoA. Morning doses will be administered at approximately 0800 hours (plus or minus 2 hours).

For BID dosing on Overall Study Day 46, Day 47, and Day 61, evening dosing of PF-06865571 and/or PF-06882961 will occur approximately 12 hours after morning dosing. On all other study days, evening dosing of PF-06865571 and/or PF-06882961 will occur approximately 10 hours after morning dosing. 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 and PF-06865571 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 as listed in the SoA and Table 4 (Part A) and Table 5 (Part B).

Table 4. Part A Dosing

Study Treatment	Drug and Dosage
Treatment A	Day 1: PF-06882961 20 mg single dose
Treatment B	Day 1: PF-06882961 20 mg single dose plus PF-06865571 300 mg single dose

Table 5. Part B Dosing

Study Period	Days in Study	Drug and Dosage
Period 1, Day 1	1	PF-06865571 300 mg single dose
Period 1, Day 2	2	No study intervention administered
Period 2, Days 1-4	3-6	PF-06882961 10 mg BID
Period 2, Days 5-8	7-10	PF-06882961 20 mg BID
Period 2, Days 9-12	11-14	PF-06882961 40 mg BID
Period 2, Days 13-16	15-18	PF-06882961 60 mg BID
Period 2, Days 17-20	19-22	PF-06882961 80 mg BID
Period 2, Days 21-24	23-26	PF-06882961 100 mg BID
Period 2, Days 25-28	27-30	PF-06882961 120 mg BID
Period 2, Days 29-32	31-34	PF-06882961 140 mg BID[a]
Period 2, Days 33-36	35-38	PF-06882961 160 mg BID[a]
Period 2, Days 37-40	39-42	PF-06882961 180 mg BID[a]
Period 2, Days 41-44	43-46	PF-06882961 200 mg BID[a]
Period 3, Day 1	47	PF-06865571 300 mg single dose plus PF-06882961 200 mg BID[a]
Period 3, Day 2	48	PF-06882961 200 mg BID[a]
Period 4, Days 1-13	49-61	PF-06865571 300 mg BID plus PF-06882961 200 mg BID[a]

Study Period	Days in Study	Drug and Dosage
Period 4, Day 14	62	No study intervention administered

a. Doses of PF-06882961 may be reduced based on PK results of Part A of this study and safety and tolerability results of Study C3421007.

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.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

The investigator will assign participant numbers to the participants as they are screened for the study. The first 4 digits of the assigned participant number will reflect the sponsor-assigned site number and the remaining 4 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 of both Part A and Part B, each participant who is dosed with 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 the sponsor's standard processes for analysis of all PK-related samples.

Participants will receive doses of PF-06882961 and PF-06865571 as described in Table 6 (Part A Sequence 1), Table 7 (Part A Sequence 2), and Table 8 (Part B).

Table 6. Part A Sequence 1 – Dosing Regimens for PF-06882961 and PF-06865571

Period	Day	AM/ PM	Dose	Number of PF-06882961 Tablets			Number of PF-06865571 Tablets	Total Number of Tablets
				10 mg	40 mg	100 mg	100 mg	
1	1	AM	20 mg PF-06882961	2				2
2	1	AM	20 mg PF-06882961 and 300 mg PF-06865571	2			3	5

Table 7. Part A Sequence 2 – Dosing Regimens for PF-06882961 and PF-06865571

Period	Day	AM/ PM	Dose	Number of PF-06882961 Tablets			Number of PF-06865571 Tablets	Total Number of Tablets
				10 mg	40 mg	100 mg	100 mg	
1	1	AM	20 mg PF-06882961 and 300 mg PF-06865571	2			3	5
2	1	AM	20 mg PF-06882961	2				2

Table 8. Part B – Dosing Regimens for PF-06882961 and PF-06865571

Period	Day(s) in Study	AM/ PM	Dose	Number of PF-06882961 Tablets			Number of PF-06865571 Tablets	Total Number of Tablets
				10 mg	40 mg	100 mg	100 mg	
1	1	AM	300 mg PF-06865571				3	3
	2	N/A	No study intervention administered					0
2	3-6	AM	10 mg PF-06882961	1				1
		PM	10 mg PF-06882961	1				1
	7-10	AM	20 mg PF-06882961	2				2
		PM	20 mg PF-06882961	2				2
	11-14	AM	40 mg PF-06882961		1			1
		PM	40 mg PF-06882961		1			1
	15-18	AM	60 mg PF-06882961	2	1			3
		PM	60 mg PF-06882961	2	1			3
	19-22	AM	80 mg PF-06882961		2			2
		PM	80 mg PF-06882961		2			2
	23-26	AM	100 mg PF-06882961			1		1
		PM	100 mg PF-06882961			1		1
	27-30	AM	120 mg PF-06882961	2		1		3
		PM	120 mg PF-06882961	2		1		3
	31-34	AM	140 mg PF-0688296[a]		1	1		2
		PM	140 mg PF-06882961[a]		1	1		2
	35-38	AM	160 mg PF-06882961[a]	2	1	1		4
		PM	160 mg PF-0688296[a]	2	1	1		4
	39-42	AM	180 mg PF-0688296[a]		2	1		3
		PM	180 mg PF-06882961[a]		2	1		3
	43-46	AM	200 mg PF-06882961[a]			2		2
		PM	200 mg PF-06882961[a]			2		2
3	47	AM	200 mg PF-06882961[a] and 300 mg PF-06865571			2	3	5
		PM	200 mg PF-06882961[a]			2		2
	48	AM	200 mg PF-06882961[a]			2		2
		PM	200 mg PF-06882961[a]			2		2
4	49-61	AM	200 mg PF-06882961[a] and 300 mg PF-06865571			2	3	5
		PM	200 mg PF-06882961[a] and 300 mg PF-06865571			2	3	5
	62	N/A	No study intervention administered					0

Period	Day(s) in Study	AM/ PM	Dose	Number of PF-06882961 Tablets			Number of PF-06865571 Tablets	Total Number of Tablets
				10 mg	40 mg	100 mg	100 mg	

a. Doses of PF-06882961 may be reduced based on PK results of Part A of this study and safety and tolerability results of Study C3421007.

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 Section 5.2 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.

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 at each clinic visit.

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

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-06882961 or PF-06865571; standard medical supportive care must be provided to manage the AEs, including administration of carbohydrates to treat HAEs (see Section 8.2.8).

6.5.1.1. Management of Nausea and Vomiting

Nausea and vomiting have been reported with administration of GLP-1 receptor agonists and also with administration of PF-06882961. 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 (eg, >120 mg BID) in Part B, titration to the next dose level may be delayed temporarily or titration to maximum tolerated dose may be permitted with Sponsor approval only.

Part B doses of PF-06882961 may be reduced in this study based on safety and tolerability results of Study C3421007. The duration of each titration step may also be revised. Part B doses of PF-06882961 may be reduced if PF-06865571 increases PF-06882961 AUC_{24} by >50% in Part A.

6.7. Stopping Rules

6.7.1. Participant Death

In the event that there is death of a participant, trial conduct will be paused and the death assessed for causality and relatedness by the medical monitor.

Sponsor will notify the FDA in the event of a participant death in accordance with IND safety reporting requirements under 21 CFR 312.32(a) and 312.32(c)(1).

6.7.2. Individual Participant Development of Adverse Events (Part B only)

If a participant experiences a severe AE, and the AE is assessed to be related to GLP-1 receptor agonist pharmacology and/or anticipated to develop toleration (eg, nausea, vomiting, anorexia), dosing may continue with protocol permitted mitigations as needed (eg, antiemetics; see Section 6.5 Concomitant Therapy). If the anticipated improvement in tolerability is not observed, the study intervention dosing will be discontinued for that participant.

If the AE is not known to be related to GLP-1 receptor agonist pharmacology, not anticipated to develop toleration, or has not yet been assessed as unrelated to study intervention, dosing of study intervention should be discontinued for the affected participant and the AE should be assessed for causality and relatedness.

6.7.3. Cohort Level Assessment of Adverse Events (Part B, Period 4 only)

During Part B (Period 4) if:

a. Three participants develop the "same" moderate AE;

   or

b. Two participants develop the "same" severe AE;

   and

c. If the AE is not known to be related to GLP-1 receptor agonist pharmacology.

The trial should be paused and AE should be assessed for causality and relatedness. If the medical team/medical monitor and investigator together deem causality to be unrelated to study intervention use, trial conduct may be continued.

If (a) or (b) occur, but not (c), ie, an AE is assessed to be related to GLP-1 receptor agonist pharmacology and/or anticipated to develop toleration (eg, nausea, vomiting, anorexia), dosing may continue with protocol permitted mitigations as needed (eg, antiemetics; see Section 6.5 Concomitant Therapy). If the anticipated improvement in tolerability is not observed, the study intervention dosing will be discontinued for that participant.

6.8. 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 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 through the follow-up contact. 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 return to the clinic for or 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. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections [redacted] may be used without repeat collection, as appropriate.

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 140 mL for Part A and approximately 525 mL for Part B. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

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

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

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

A complete physical exam will be done at time points specified in the SoA, otherwise, brief exam will be conducted 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

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements. When 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 PR 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.

8.2.3. 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 QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTc interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc 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 QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTc interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTc 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 QTc 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 (Part B only)

The C-SSRS is an interview based rating scale to systematically assess suicidal ideation and suicidal behavior.[24] 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 (Part B only)

The PHQ-9 is a 9 item self-report scale for the assessment of depressive symptoms.[25] 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 2 or more occasions 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. COVID-19 Specific Assessments

Participants will be tested for COVID-19 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 required by local regulations or by the Principal Investigator.

8.2.7. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study interventions. 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.

8.2.8. 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 CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.2.8.1 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.

8.2.8.1. 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:[27]

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.

8.2.9. Glucometer Monitoring of Glucose

Monitoring of 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.

8.3. 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 of study intervention.

- 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

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

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

Medication errors include:

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

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

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

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

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

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.

Any dose of PF-06865571 greater than 1800 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose for PF-06882961 or PF-06865571. 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 or PF-06865571 (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 PF-06882961, CCI and PF-06865571 (Part B only) 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 measurement of plasma concentrations of PF-06882961, CCI and PF-06865571 will be analyzed using validated analytical methods in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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

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

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. Plasma for Analysis of PF-06882961 CCI [redacted]

Blood samples of approximately 3 mL, to provide a minimum of approximately 1.2 mL plasma, will be collected for measurement of plasma concentrations of PF-06882961 CCI [redacted] 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.

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

8.5.2. Plasma for Analysis of PF-06865571

Blood samples of approximately 3 mL, to provide a minimum of approximately 1.2 mL plasma, will be collected for measurement of plasma concentrations of PF-06865571 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.

Samples will be used to evaluate the PK of PF-06865571. Samples collected for analyses of PF-06865571 plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted].

CCI [redacted].

CCI [redacted].

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

8.8.5. Plasma for Analysis of CP-I (Part B only)

Blood samples of approximately 3 mL, to provide a minimum of approximately 1.2 mL plasma, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of CP-I at times specified in the SoA. Samples collected for measurement of plasma concentrations of CP-I will be analyzed using a validated analytical method in compliance with applicable SOPs. Instructions for the collection and handling of biological samples will be provided in the laboratory manual.

8.8.6. Plasma for 4-β-hydroxycholesterol/cholesterol Analysis (Part B only)

Blood samples of approximately 4 mL, to provide a minimum of approximately 1.6 mL plasma, will be collected into appropriately labeled tubes containing lithium heparin for the analysis of 4-β-hydroxycholesterol and cholesterol at times specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual.

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

9.2.1. Sample Size for Part A

Approximately 8 participants will be enrolled in Part A of this study. The expected widths of the 90% confidence intervals with 80% coverage probability for these comparisons are shown in Table 9 for a range of possible effects based on sample sizes of 6, 8, and 10 participants. These estimates are based on an assumed standard deviation of 0.200 in $\log_e AUC_{24}$ for PF-06882961 obtained from an internal single ascending dose study.

Table 9. Estimated Effect of PF-06865571 on PF-06882961 in Part A – Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects and Parameters of Interest

Parameter	N	Estimated Effect (Test/Reference)	AUC_{24}	
			Probable 90% CI	Probable CI Width
AUC_{24} (PF-06882961)	6	100%	74 to 135%	61%
		150%	111 to 203%	92%
		200%	148 to 270%	122%
	8	100%	79 to 126%	47%
		150%	119 to 189%	70%
		200%	159 to 252%	94%
	10	100%	82 to 122%	39%
		150%	123 to 182%	59%
		200%	165 to 243%	79%

9.2.2. Sample Size for Part B

A sample size of approximately 16 participants will be enrolled in Part B such that approximately 12 evaluable participants complete the study.

To characterize the effect of PF-06865571 on PF-06882961 PK parameters, the expected widths of the 90% confidence intervals with 80% coverage probability for these comparisons are shown in Table 10 for a range of possible effects based on sample sizes of 12, 14, and 16 participants. These estimates are based on an assumed standard deviation of 0.308 in $\log_e AUC_{24}$ for PF-06882961 obtained from an internal multiple ascending dose study. These estimates also assume similar variability between AUC_{12} and AUC_{24}.

Table 10. Estimated Effect of PF-06865571 on PF-06882961 in Part B – Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects and Parameters of Interest

Parameter	N	Estimated Effect (Test/Reference)	AUC_{24}	
			Probable 90% CI	Probable CI Width
AUC_{24} (PF-06882961)	12	50%	39% to 65%	26%
		75%	58% to 97%	40%
		100%	77% to 130%	53%
	14	50%	40% to 63%	24%
		75%	59% to 95%	36%
		100%	79% to 127%	48%
	16	50%	40% to 62%	22%
		75%	60% to 93%	33%
		100%	81% to 124%	44%

To characterize the effect of PF-06882961 on PF-06865571 PK parameters, the expected widths of the 90% confidence intervals with 80% coverage probability for these comparisons are shown in Table 11 for a range of possible effects based on sample sizes of 12, 14, and 16 participants. These estimates are based on an assumed conservative standard deviation of 0.12 in $\log_e AUC_{inf}$ for PF-06865571 obtained from an internal single ascending dose study.

Table 11. Estimated Effect of PF-06882961 on PF-06865571 in Part B – Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects and Parameters of Interest

Parameter	N	Estimated Effect (Test/Reference)	AUC_{inf}	
			Probable 90% CI	Probable CI Width
AUC_{inf} (PF-06865571)	12	100%	90% to 111%	20%
		125%	113% to 138%	25%
		150%	136% to 166%	30%
		200%	181% to 221%	41%

	14	100%	91% to 110%	18%
		125%	114% to 137%	23%
		150%	137% to 164%	28%
		200%	182% to 219%	37%
	16	100%	92% to 109%	17%
		125%	115% to 136%	21%
		150%	138% to 163%	25%
		200%	184% to 218%	34%

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 PF-06882961 and/or PF-06865571 and in whom at least 1 plasma concentration value is reported.

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 and Endogenous Biomarker Parameters

PK parameters for PF-06882961, CCI [redacted] and PF-06865571 (Part B only) will be derived (if data permit) from the plasma concentration-time data using standard noncompartmental methods for Part A and Part B as defined in Table 12 and Table 13, respectively. AUC_{12} and C_{max} for CP-I in Part B will be derived (Table 13). Plasma 4-β-hydroxycholesterol/cholesterol at each collection time in Part B will also be calculated. Actual PK sampling times will be used in the derivation of PK parameters.

Table 12. Part A – Plasma PK Parameters for PF-06882961

Parameter	Definition	Method of Determination
AUC_{24}	Area under the plasma concentration-time curve from time 0 to time 24 hours post-dose	Linear/log trapezoidal method
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence

Table 13. Part B – Plasma PK Parameters for PF-06882961, CCI and PF-06865571, and Plasma CP-I Parameters

Parameter	Compound	Day	Definition	Method of Determination
AUC_{last}	PF-06865571	1 and 47	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (C_{last}).	Linear/log trapezoidal method.
AUC_{inf}*	PF-06865571	1 and 47	Area under the plasma concentration-time curve 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.
AUC_{12}	PF-06865571	61	Area under the plasma concentration-time curve from time 0 to time 12 hours post-dose.	Linear/log trapezoidal method.
	PF-06882961 CCI	46 and 61		
	CP-I	30 and 46		
C_{max}	PF-06865571	1, 47, and 61	Maximum plasma concentration.	Observed directly from data.
	PF-06882961 CCI	46 and 61		
	CP-I	30 and 46		
T_{max}	PF-06865571	1, 47, and 61	Time for C_{max}.	Observed directly from data as time of first occurrence.
	PF-06882961 CCI	46 and 61		
$t_{1/2}$*	PF-06865571	1 and 47	Terminal half-life.	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.

Parameter	Compound	Day	Definition	Method of Determination
				Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F*	PF-06865571	1 and 47	Apparent oral clearance.	Single Dose = Dose/AUC_{inf};
	PF-06882961	46 and 61		Multiple Dose = Dose/AUC_{12}
Vz/F*	PF-06865571	1 and 47	Apparent oral volume of distribution.	Single Dose = Dose/(AUC_{inf}*k_{el});
[redacted]				

* If data permit.

9.4.2. Statistical Methods for Pharmacokinetic Data

The PK parameters listed in Table 12 and Table 13 will be summarized descriptively for Part A and Part B by treatment as applicable for each analyte.

9.4.2.1. Part A – Statistical Methods for Pharmacokinetic Data

Plasma concentrations of PF-06882961 will be listed and summarized descriptively by PK sampling time and treatment (dosing alone versus 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 C_{max} and AUC_{24} of PF-06882961 administered alone or co-administered with PF-06865571 will be analyzed using a mixed effect model with treatment, sequence, and period as a fixed effects and participant embedded in sequence 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 reference treatment will be “PF-06882961 20 mg” administered alone, whereas the test treatment will be “PF-06882961 20 mg plus PF-06865571 300 mg BID”.

9.4.2.2. Part B – Statistical Methods for Pharmacokinetic and Endogenous Biomarker Data

Plasma concentrations of PF-06882961, CCI PF-06865571, and CP-I will be listed and summarized descriptively by sampling time and treatment (dosing alone versus 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 C_{max}, AUC_{last}, and AUC_{inf} (as data permit) of PF-06865571 300 mg BID 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 test treatment will be "PF-06865571 300 mg plus PF-06882961 200 mg BID" (Period 3), which will be reported separately in comparison to the reference treatment of "PF-06865571 300 mg" (Period 1).

Natural log-transformed AUC_{12} and C_{max} of PF-06882961 200 mg BID administered alone or co-administered with PF-06865571 300 mg BID will be analyzed and reported separately using the same mixed effect model as described above. The test treatment will be "PF-06865571 300 mg BID plus PF-06882961 200 mg BID" (Period 4), which will be reported separately in comparison to the reference treatment of "PF-06882961 200 mg BID administered alone" (Period 2).

The above and other PK parameters for PF-06865571, and PK parameters for PF-06882961, will be separately summarized descriptively by treatment.

The mean of CP-I plasma concentrations on Day 1 will serve as baseline.

Change from baseline in $AUC_{12}/12$ and C_{max} for CP-I 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 against the reference will be obtained and corresponding 90% CIs will be reported from the models. The test treatments will be "PF-06882961 120 mg BID" (Day 30) and "PF-06882961 200 mg BID" (Day 46) and reference treatment is "No PF-06882961" (Day 1). Additionally, AUC_{12}, $AUC_{12}/12$ and C_{max} for CP-I will be separately summarized descriptive by treatment.

The plasma 4-β-hydroxycholesterol/cholesterol ratios will be summarized descriptively by day. Individual subject and median plots will be produced by day (Days 1, 19, 31, and 47). Percent change of the 4-β-hydroxycholesterol/cholesterol ratio from baseline will be summarized descriptively by day.

9.4.3. Safety Analyses

All safety analyses will be performed on the safety population.

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

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

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

9.4.3.1. Electrocardiogram Analyses

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

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

Safety QTcF Assessment

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

In addition, an attempt may be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship may be examined. If the exposure-QT analyses is performed, it will be reported separately, not as part of the CSR.

9.4.4. Other Analyses

Tertiary/exploratory analyses not included in the PK or safety analyses outlined above will be documented in the SAP.

CCI [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 dose-escalation decisions, 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

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

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

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

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

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

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.

A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

The following data types collected post-screening visit may be recorded directly on the CRFs (ie, for which there is no existing written or electronic record of data) and is to be considered source data:

- Prior and concomitant treatments;
- Non-drug treatments;
- Serious and non-serious adverse events;
- Hypoglyemic adverse events;
- Medication errors;
- Body weight;
- Vital signs (blood pressure and pulse rate);
- Study intervention dosing administration;
- Safety laboratory sample collection;
- CCI [redacted]
- PK blood sample collection;
- Participant disposition;
- Withdrawal of consent.

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

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

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 14. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine eGFR[a] Cystatin-C eGFR, using CKD-EPI-Cystatin-C[b] 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	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[c]	COVID-19 testing Serum pregnancy test (β-hCG)[d] Urine drug screening[e] Lipid panel: • Total cholesterol • Direct LDL-C • HDL-C • Triglycerides TSH Free T4 Calcitonin Amylase Lipase ***Serum*** total bile acids PT/INR/aPTT <u>At screening only:</u> • HbA1c • FSH[f] • HIV • HepBsAg • HCVAb • HCV RNA

a. Part A – all safety assessment timepoints and Part B – Screening only.
b. Part B – all safety assessment timepoints beyond Screening.
c. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
d. Serum β-hCG for all WOCBP.
e. The minimum requirement for drug screening includes cocaine, THC, opiates, opioids, benzodiazepines, and amphetamines (others are site and study specific).
f. For confirmation of postmenopausal status only.

Investigators must document their review of each laboratory safety report.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the 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 <u>Meeting</u> the AE Definition

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

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

10.3.2. Definition of SAE

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

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

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

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

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies for both PF-06882961 and PF-06865571.

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 risks 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).

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

Potential Cases of Drug-Induced Liver Injury

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

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.9.1. Eligibility

COVID-19 testing is mandated for this study. A patient should be excluded if he/she has a positive test result for COVID-19 infection, is known to have asymptomatic infection, or is suspected of having COVID-19.

10.9.2. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. It is recommended that the investigator consult the study medical monitor regarding how to manager study intervention, including termporary or permanent discontinuation of study intervention.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
Abs	absolute
ACC	acetyl-CoA carboxylase
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{12}	area under the plasma concentration-time curve from time zero to time 12 hours post-dose
AUC_{24}	area under the plasma concentration-time curve from time zero to time 24 hours post-dose
AUC_{inf}	area under the plasma concentration-time curve from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (C_{last})
AV	atrioventricular
CCI	CCI
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
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
CL/F	apparent oral clearance
C_{last}	time of the last quantifiable concentration
C_{max}	maximum plasma concentration
CP-I	coproporphyrin I
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease-19
CRF	case report form
CRO	contract research organization
CRU	clinical research unit

Abbreviation	Term
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
CV	coefficient of variation
CYP	cytochrome P450
DAG	diacylglycerol
DC	discontinuation
DDI	drug-drug interaction
DGAT	diacylglycerol acyltransferase
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
CCI	[redacted]
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
f_m	fraction metabolized
FAP	final approved protocol
FDA	Food and Drug Administration
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
F/U	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide 1
HAE	hypoglycemic adverse event
HbA1c	hemoglobin A1c
HepBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HDL-C	high density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate

Abbreviation	Term
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
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(ly)
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
k_{el}	elimination rate constant
K_i	apparent inactivation constant at half-maximal rate of inactivation
k_{inact}	maximal inactivation rate
LBBB	left bundle branch block
LDL-C	low density lipoprotein cholesterol
LFT	liver function test
LLN	lower limit of normal
MATE	multidrug and toxin extrusion protein
mBcrp	mouse breast cancer resistance protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	multi-drug resistance
MEN2	multiple endocrine neoplasia syndrome type 2
MHP	mental health professional
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mRNA	messenger ribonucleic acid
msec	millisecond
MTD	maximum tolerated dose
N/A	not applicable
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NCE	new chemical entity
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PCR	polymerase chain reaction
PD	pharmacodynamics

Abbreviation	Term
P-gp	P-glycoprotein
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetics
PLT	platelet
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction/complex
Q8H	every 8 hours
Q12H	every 12 hours
QT	time from beginning of the QRS complex to the end of the T wave
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
R_{ac}	accumulation ratio
RBC	red blood cells
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
T4	thyroxine
TBA	total bile acids
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TG	triglycerides
THC	tetrahydrocannabinol
TSH	thyroid-stimulating hormone
T_{max}	time for C_{max}
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
V_z/F	apparent oral volume of distribution
WBC	white blood cell
WOCBP	woman of childbearing potential

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