A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE STUDY TO EVALUATE THE EFFECT OF ITRACONAZOLE AND CYCLOSPORINE ON THE SINGLE-DOSE PHARMACOKINETICS OF PF-07081532 IN OVERWEIGHT OR OBESE ADULT PARTICIPANTS

Study Intervention Number:	PF-07081532
Study Intervention Name:	NA
US IND Number:	CCI
EudraCT/EU CT Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C3991041
Phase:	1
Brief Title: A Drug-Drug Interaction Study to Examine the Impact of Itraconazole and Cyclosporine on PF-07081532 Pharmacokinetics in Overweight or Obese Adult Participants.	

Document History

Document	Version Date
Original protocol	31 January 2023

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Open-Label, Fixed-Sequence Study to Evaluate the Effect of Itraconazole and Cyclosporine on the Single-Dose Pharmacokinetics of PF-07081532 in Overweight or Obese Adult Participants.

Brief Title: A Drug-Drug Interaction Study to Examine the Impact of Itraconazole and Cyclosporine on PF-07081532 Pharmacokinetics in Overweight or Obese Adult Participants.

Regulatory Agency Identification Number(s):

US IND Number:	CCI
EudraCT Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C3991041
Phase:	1

Rationale: This is a Phase 1, open-label, fixed-sequence study to evaluate the effect of multiple doses of itraconazole and a single dose of cyclosporine on the single-dose PK of PF-07081532 in otherwise healthy, overweight or obese adult participants and to generate safety, tolerability, and PK data for further clinical development.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effect of MD itraconazole on the SD PK of PF-07081532 in otherwise healthy, overweight or obese participants.	• PF-07081532 PK parameter: AUC_{inf} (if data permit[a] otherwise AUC_{last})
• To estimate the effect of SD cyclosporine on the SD PK of PF-07081532 in otherwise healthy, overweight or obese participants.	• PF-07081532 PK parameter: AUC_{inf} (if data permit[a] otherwise AUC_{last})
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-07081532 administered separately and in combination with itraconazole or cyclosporine in otherwise healthy, overweight or obese participants.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To evaluate the effects of itraconazole or cyclosporine on additional PK parameters for PF-07081532.	• Additional plasma PK parameters for PF-07081532: C_{max} and T_{max}; and CL/F, V_z/F, $t_{½}$, as data permit.

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

Overall Design:

This is a Phase 1, open-label, fixed-sequence, 3-period study to evaluate the effect of multiple doses of itraconazole and a SD of cyclosporine on the single-dose PK of PF-07081532 in otherwise healthy, overweight or obese, adult female and male participants. The 3 study periods will be conducted consecutively without a break.

Number of Participants:

Approximately 16 participants will be enrolled in the study such that approximately 12 evaluable participants complete the study.

Note: "Enrolled" means a participant's or their legally authorized representative's agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. 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.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Otherwise healthy female and male participants must be at least 18 years of age at the time of signing the ICD (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, physical examination, including blood pressure and pulse rate measurement, standard 12-lead ECG and clinical laboratory tests).

    - Women can be of child-bearing potential, but cannot be pregnant, breastfeeding, or planning to become pregnant while participating in the study, may not be taking either oral contraceptives or non-oral hormonal contraceptives (with the exception of implantable progestogen only or intrauterine hormone releasing system), and must avoid vaccination with live attenuated vaccines.

2. BMI: $\geq$25.0 kg/m^2 at Screening.

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

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

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).

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

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

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

    - Known hypersensitivity to itraconazole or cyclosporine.

2. 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.

3. 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). Anyone with any history of pancreatic CA will be excluded, even if it was resected and they were considered 'cured'.

4. Personal or family history of MTC or MEN2, or study participants with suspected MTC per the investigator's judgment.

5. Acute pancreatitis, a history of repeated episodes of acute pancreatitis, or history of chronic pancreatitis.

6. Symptomatic gallbladder disease.

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

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

9. Known medical history of active liver disease, including chronic hepatitis B or C, primary biliary cirrhosis, alcoholic liver disease, primary sclerosing cholangitis, autoimmune hepatitis, overlap syndrome, or prior known drug-induced liver injury.

10. History of HIV infection.

11. Any lifetime history of a suicide attempt.

12. Use of any medications that are:

    - Moderate or strong CYP3A4/5 and/or CYP2C19 inhibitors within 14 days or 5 half-lives (whichever is longer),

    - Moderate or strong CYP3A and/or CYP2C19 inducers within 14 days or 5 half-lives (whichever is longer), or

    - Systemic therapy with inhibitors of OATP transporters within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention.

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

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

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

15. 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 level ≥1.25 × ULN.

- Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.
- TSH >1.5 × ULN or <LLN.
- Serum calcitonin > ULN.
- Amylase or lipase > ULN.
- Fasting blood glucose ≥126 mg/dL.
- Fasting C-peptide not within normal limit.
- eGFR <75 mL/min/1.73 m^2 as calculated by the CKD-EPI equation.

Study Arms and Duration:

The total duration of participation from the Screening Visit to the F/U telephone contact will be approximately 82 days or 12 weeks, approximately 3 weeks of which will be conducted on an inpatient basis. The 21-day inpatient portion of the study will be conducted as follows:

Period 1: Days -1 to 5 (Study Days -1 to 5; participants are admitted to the CRU on Day -1), 40 mg SD PF-07081532 on Day 1;

Period 2: Days 1 to 5 (Study Days 6 to 10), 40 mg SD PF-07081532 plus 600 mg SD cyclosporine on Day 1;

Period 3: Days 1 to 10 (Study Days 11 to 20; participants are discharged from the CRU on Study Day 20), 200 mg itraconazole QD ×9 days plus 40 mg SD PF-07081532 on Day 4.

A telephone F/U contact will occur 28-35 days from the last dose of study intervention (Period 3, Day 9).

Study Intervention(s)			
Intervention Name	PF-07081532	Itraconazole	Cyclosporine
Arm Name (group of participants receiving a specific treatment or no treatment)	All participants	All participants	All participants
Unit Dose Strength	20 mg	10 mg/mL	100 mg
Route of Administration	Oral	Oral	Oral

Study Intervention(s)			
Use	Substrate	Perpetrator	Perpetrator
IMP or AxMP	IMP	AxMP	AxMP

Study Arm(s)			
Arm Title	Period 1: PF-07081532 single dose	Period 2: Cyclosporine + PF-07081532	Period 3: Itraconazole + PF-07081532
Arm Type	No intervention	Experimental (DDI)	Experimental (DDI)
Arm Description	Participants will receive PF-07081532 as a single 40 mg dose on Day 1.	Participants will receive a single 40 mg dose of PF-07081532 and a single 600 mg dose of cyclosporine on Day 1.	Participants will receive itraconazole 200 mg QD × 9 days plus a single 40 mg dose of PF-07081532 on Day 4.

No dose adjustments or reductions will be permitted in this study.

Statistical Methods:

Approximately 12 evaluable participants will complete the study.

Natural $\log_e$ transformed AUC_{inf} of PF-07081532 administered without cyclosporine or coadministered with cyclosporine 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% CIs will be obtained from the models. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. The test treatment will be 'PF-07081532 40 mg SD and cyclosporine' (Period 2), which will be reported separately in comparison to the reference treatment of 'PF-07081532 40 mg SD without cyclosporine' (Period 1).

Natural $\log_e$ transformed AUC_{inf} of PF-07081532 administered without itraconazole or coadministered with itraconazole 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% CIs will be obtained from the models. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. The test treatment will be 'PF-07081532 40 mg SD and itraconazole' (Period 3), which will be reported separately in comparison to the reference treatment of 'PF-07081532 40 mg SD without itraconazole' (Period 1).

Ethical Considerations:

PF-07081532 is not expected to provide any long-term clinical benefit to the healthy adult female and male participants in this study. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development.

Based on experience with PF-07081532 and other marketed GLP-1R agonists, the potential risks for PF-07081532 include thyroid C-cell tumors, pancreatitis, hypoglycemia, renal function impairment, gastrointestinal adverse reactions, suicidal ideation and behavior, changes in heart rate and blood pressure, weight loss, and/or acute gallbladder disease.

Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants of childbearing potential must agree to use appropriate contraception methods and avoid vaccination with live attenuated vaccines.

1.2. Schema

Not applicable.

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 infonnation 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 paiiicipant.

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be fonnd in Annendix 9.	**Scr·een**	**Period 1**		**Period 2**	**Period 3**	**F/U (Phone Call)**	**ET**	**Notes**
Study Day		**-1**	**Ito5**	**6to 10**	**11 to 20**	47 to 54		
Days Relative to Day 1	**D-28 to D-2**	**D-1**	**Dl toD5**	**Dl to D5**	**Dl to DlO**	**28-35 Days**		1. All screening should be done '.S28 days before the first dose. 2. Day relative to start of study intervention (Day 1). 3. In this study, follow-up is to be conducted via phone contact 28 to 35 days after administration of the final dose of study intervention (Period 3 Dav 9, Studv Dav 19).
Info,med consent	**X**							• Info,med consent should be obtained prior to nndergoing any study-specific procedm·es.
CRU confinement		**X**	→	→	**X**			
Inclusion/exclusion criteria	**X**	**X**						
Medical/medication histo,y	**X**	**X**				**X**		• Including histo,y collection of alcohol and tobacco use.
Physical exam	**X**	**X**						• Complete PE conducted at Screening or admission, and as required at PI' s discretion.
Bodyweight	**X**	**X**	X(D5)	X(D5)	X (DlO)		**X**	

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Safety laborato,y (hematology, chemistiy, and UA)	X	X		X(D5 chemistiy only)	X		X	• See Table 5 for a complete list of clinical lab tests. • Period 3 collection prior to discharge on Day 10.
Calcitonin, amylase, lipase, HbAlC, TSH, C-Peptide	X							• An ovemight fast is required prior to calcitonin sample collection.
Demography	X							• Including height and weight.
Serum and urine pregnancy test (WOCBP only)	X	X			X (DlO)		X	• Pregnancy tests will also be done whenever 1 menstmal cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the studv nrior to discharoe on Period 3 Dav 10.
Contraception check	X	X				X	X	
FSH	X							• For any female who has been ameno1Theic for at least 12 consecutive months.
Urine dmg testing	X	X						• Participants may undergo random mine dmg testing at the discretion of the investigator.
Single 12-Lead ECG	X		X	X	X		X	• Pre-dose Day 1 in each period, and prior to discharge on Period 3 Day 10.
Blood pressure, pulse rate, and body temperature	X		X	X	X		X	• Pre-dose Day 1 in each period, and prior to discharge on Period 3 Day 10. • Bodv temoerattu·e will be taken at Sreenin onlv.

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Visit Identifiel' Abbreviations used in this table may be fonnd in A endix 9.	Scr·een	Period 1		Period 2	Period 3	F/U (Phone Call)	ET	Notes
Study Day		-1	Ito5	6to 10	11 to 20	47 to 54		
Days Relative to Day 1	D-28 to D-2	D-1	Dl toD5	Dl to D5	Dl to DlO	28-35 Days		1. All screening should be done '.S28 days before the first dose. 2. Day relative to start of study intervention (Day 1). 3. In this study, follow-up is to be conducted via phone contact 28 to 35 days after administration of the final dose of study intervention (Period 3 Da 9. Stud Da 19 .
HIV, HBsAg, HBcAb, HCV RNA,HCVAb	X							
C-SSRS and PHQ-9	X	X			X (Dl0)		X	
COVID-19 assessments		X						• See Section 8.3.5.
Study intervention administration PF-07081532			X(D1)	X(Dl)	X(D4)			• See Table 2 and Table 3 for specifics.
Study intervention administration itra conazole					X (Dl-9)			• See Table 3.
Study intervention administration cyclosporine				X(Dl)				• See Table 2.
Pha1macokinetic blood sampling: PF-07081532			D1-5	D1-5	D4-10		X	• See blood sampling timepoints in Table 2 for Periods 1 and 2 and Table 3 for Period 3.
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CCI								

Table 1. Study Schedule of Assessment

Visit Identifiel' Abbreviations used in this table may be fonnd in Aooendix 9.	**Scr·een**	**Period 1**		**Period 2**	**Period 3**	**F/U (Phone Call)**	**ET**	**Notes**
Study Day		**-1**	**Ito5**	**6to 10**	**11 to 20**	47 **to 54**		
Days Relative to Day 1	**D-28 to D-2**	**D-1**	**Dl toD5**	**Dl to D5**	**Dl to DlO**	**28-35 Days**		1. All screening should be done '.S28 days before the first dose. 2. Day relative to start of study intervention (Day 1). 3. In this study, follow-up is to be conducted via phone contact 28 to 35 days after administration of the final dose of study intervention (Period 3 Dav 9. Studv Dav 19).
CRU discharge					X (DlO)			
Serious and nonserious AE monitoring	**X**	➔	➔	➔	➔	➔	➔	• See Section 8.4.3 for follow-up AE and SAE assessments.

Table 2. PK Blood Sampling - Periods 1 and 2

Visit Identifier	**Periods 1 and 2**																**Notes**
Period Day	**1**										**2**		**3**	**4**	**5**		
Hours After Dose	**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**24**	**36**	**48**	**72**	**96**	**120**	• Hour 0 = predose sample collection. • The 120-hour PK samples in Periods 1 and 2 are the same as the 0-hour PK samples in Periods 2 and 3, respectively.
Study intervention administration PF-07081532	X																
Study intervention administration cyclosporine ***(Period 2 only)***	X																
PK blood sampling PF-07081532	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 3. PK Blood Sampling – Period 3

Visit Identifier	**Period 3**																				**Notes**
Period Day	**1**	**2**	**3**	**4**										**5**		**6**	**7**	**8**	**9**	**10**	
Hours After Dose				**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	Hour 0 = predose sample collection
Study intervention administration PF-07081532				X																	
Study intervention administration itraconazole	X	X	X	X										X		X	X	X	X		
PK blood sampling				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

2. INTRODUCTION

GLP-1 is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake.[1] GLP-1 activation of the GLP-1R stimulates insulin release, inhibits glucagon secretion in a glucose-dependent manner, and delays gastric emptying.[2,3] In addition, GLP-1 has been shown to increase satiety and suppress food intake.[4]

PF-07081532 is an orally administered, potent and selective GLP-1R agonist in development as adjunct to diet and exercise, to improve glycemic control in T2DM, and for chronic weight management in a population that is overweight with co-morbidities or who have obesity.

2.1. Study Rationale

In vitro data indicate that PF-07081532 is a substrate for both CYP3A and OATP; therefore, an assessment of the impact of inhibition of these pathways is needed. This study will evaluate the impact of the strong CYP3A inhibitor, itraconazole, and the OATP inhibitor, cyclosporine, on the single-dose PK of PF-07081532.

The purpose of this Phase 1, open-label, fixed-sequence study is to evaluate the effect of multiple doses of itraconazole and a single dose of cyclosporine on the SD PK of PF-07081532 in otherwise healthy, overweight or obese adult participants, and to generate safety, tolerability, and PK data for further clinical development.

2.2. Background

T2DM is estimated to affect more than 424 million people worldwide,[5] and the prevalence of T2DM within the US is estimated to range from 12 to 14%.[6] Patients with poorly controlled T2DM have an increased risk of developing complications associated with both microvascular and macrovascular disease, including nephropathy, neuropathy, retinopathy, cardiovascular disease and stroke; and are at 2 to 4 times increased risk of mortality than adults who do not have diabetes.[7] While existing pharmacological options for the treatment of diabetes may provide satisfactory glycemic control for some patients, there remains a large number of patients who do not achieve target glycated HbA1c levels, suggesting a need for additional therapeutic options.

Obesity is a chronic disease that is associated with serious co-morbidities, including T2DM, dyslipidemia, hypertension, atherosclerosis, obstructive sleep apnea and certain cancers,[8] and is also associated with increased all-cause mortality.[9] The global burden of obesity is high with more than 600 million adults estimated to have obesity worldwide. In addition, the prevalence of obesity has doubled in more than 70 countries since 1980 and poses a major public health challenge.[10] First line treatment for obesity is lifestyle intervention including diet, exercise and behavioral therapy. While effective in many patients, lifestyle intervention is often not sustainable, and many patients regain weight after initial weight loss.[11] Pharmacotherapy has been approved for the long-term treatment of obesity and can be a useful adjunct to lifestyle intervention to augment and maintain weight loss.

Marketed injectable GLP-1R agonists have demonstrated robust glycemic efficacy, weight loss, and cardiovascular safety, with more than one marketed agent demonstrating

cardiovascular benefit.[12] Based on the clinical experience with injectable GLP-1R agonists, an oral, small molecule GLP-1R agonist is expected to improve glucose control and reduce HbA1c levels in patients with T2DM, and to decrease appetite and body weight, resulting in weight loss in patients with T2DM and obesity, while avoiding the subcutaneous injection required by currently available peptidic GLP-1R agonists.

2.2.1. Nonclinical Pharmacology

Refer to the IB for details on the nonclinical pharmacology of PF-07081532.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

In rats and monkeys following single IV and oral dosing, PF-07081532 exhibited low CL_p (13 and 0.6 mL/min/kg, respectively), with low to moderate steady-state V_{ss} (0.76 and 0.21 L/kg, respectively), leading to a $t_{½}$ of 1.6 hours in rats and 8.8 hours in monkeys. Renal excretion was negligible in both species, and biliary excretion was minimal in rats. The systemic exposure (assessed by AUC and C_{max}) of PF-07081532 following oral repeat doses generally increased in a dose-proportional manner.

In vitro, PF-07081532 was a substrate for the hepatic uptake transporter, OATP1B3, but not for OATP1B1. Coadministration of an OATP inhibitor with PF-07081532 in monkeys resulted in a notable increase in the plasma AUC exposure of PF-07081532 and corresponding decrease in CL, suggesting a potential role for OATP transport in the uptake limited CL in monkeys.

PF-07081532 was extensively metabolized via oxidative CYP and conjugation UGT pathways. CYP-mediated metabolism accounted for 67% of the hepatic metabolism, with CYP3A (31%) being the predominant CYP isoform. The contribution of non-CYP metabolism was estimated to be 33% of the hepatic metabolism, which was due to glucuronidation (24%) and chemical hydrolysis (9%). UGT1A1 and UGT1A3 were primarily responsible for the glucuronidation of PF-07081532, with possible minor contributions by the non-hepatic UGT isoforms, UGT1A7 and UGT1A8.

Refer to the IB for more details on the nonclinical PK and metabolism of PF-07081532.

2.2.3. Nonclinical Safety

PF-07081532 has been evaluated in a comprehensive nonclinical safety package that includes toxicity studies up to 6 months (in rats) and 9 months (in monkeys), as well as reproductive and developmental toxicology studies in rats and rabbits. Based on the nonclinical studies conducted, the target organs and systems identified with PF-07081532 administration include the heart, stomach and liver.

In the 6-month pivotal study with 1-month recovery phase in rats, oral gavage administration of PF-07081532 for 6 months did not result in any mortality or adverse effects in any of the study parameters or endpoints evaluated resulting in the high dose being the NOAEL. The exposure at this dose provided exposure margins of 40× and 29× (C_{max} and AUC_{24}, respectively) over the highest clinical dose planned (260 mg QD).

In the 9-month pivotal study in cynomolgus monkeys, PF-07081532 was administered by oral gavage with doses titrating up. There were no adverse findings in the endpoints evaluated in this study. The primary effects were consistent with the expected pharmacology of the test article which included decreased body weight associated with decreased food consumption, and secondary changes in clinical chemistry and hematology parameters. At the NOAEL dose, the exposure margins were 5.2× and 4.6× (C_{max} and AUC_{24}, respectively) over the highest clinical dose (260 mg QD) planned.

The NOAELs in the 6-month rat or 9-month monkey pivotal toxicity studies were 100 mg/kg/day in both species, with associated unbound C_{max} of 768 ng/mL and unbound AUC_{24} of 8270 ng•h/mL in rats and unbound C_{max} of 98.5 ng/mL and unbound AUC_{24} of 1300 ng•h/mL in monkeys.

PF-07081532 was not genotoxic in either in vitro or in vivo assays. In addition, PF-07081532 was negative in the 3T3 Neutral Red uptake Phototoxicity Test, indicating that PF-07081532 is not phototoxic.

Refer to the IB for more details on the nonclinical safety of PF-07081532.

2.2.4. Clinical Overview

As of issuance of this protocol, 2 Phase 1 studies evaluating PF-07081532 (C3991001 and C3991002) have been completed. In total, 88 participants have been randomized, including 22 healthy adult participants, 51 adult participants with T2DM, and 15 adult participants with obesity. A total of 74 unique participants have been exposed to at least 1 dose of PF-07081532. The safety profile of PF-07081532 was assessed in these 2 completed clinical studies and, to date, administration of PF-07081532 at single doses up to 200 mg and multiple doses up to 180 mg QD has been considered safe, with the majority of the TEAEs being mild in intensity.

One Phase 1 study, C3991003, recently concluded. This inpatient study enrolled participants with T2DM inadequately controlled on metformin, and participants with obesity, to receive PF-07081532 or placebo QD for 42 days. The starting dose for the first cohort of this study was 20 mg QD of PF-07081532, with subsequent dose levels determined based on emerging data; the maximum dose administered was 80 mg QD. While final clinical data from this study are not yet available, as of issuance of this protocol, there have been no deaths, SAEs or AEs of severe intensity reported.

Refer to the IB for more details on the clinical safety of PF-07081532.

2.2.4.1. Clinical Pharmacokinetics

The clinical PK of PF-07081532 in adult participants have been evaluated to date in 2 completed studies (C3991001 and C3991002). The results of these completed studies are summarized in the PF-07081532 IB.

In Study C3991001 following administration of single oral doses of PF-07081532 under fasted conditions to healthy participants, PF-07081532 was absorbed relatively rapidly with a

median T_{max} of 1.00 to 4.02 hours (individual T_{max} values ranged between 0.5 and 6 hours). Based on the individual plasma concentration-time profiles, the absorption phase exhibited multiple peaks, especially at the higher dose levels. Mean $t_{½}$ ranged from 18.03 to 20.90 hours across all doses. Plasma C_{max} increased less than proportionally across the entire investigated dose range (from 10 mg to 200 mg), while plasma AUC_{inf} increased less than proportionally from 10 mg to 30 mg and approximately proportionally from 30 mg to 200 mg. Inter-participant variability for PF-07081532 exposure was low to moderate and ranged from 9% to 36% CV for C_{max} and 15% to 44% CV for AUC_{inf} across all doses. Overall, the results indicate that PF-07081532 may be administered without regard to food.

In Study C3991002 following administration of PF-07081532, C_{max} was observed at 1 to 2 hours on Day 1, and 2 to 8 hours following the last dose on Day 28 or 42. Across all dose groups, the mean $t_{½}$ ranged from 20.70 to 26.50 hours. PF-07081532 exposure generally increased in an approximately dose-proportional manner across the dose range studied, and accumulation of less than 2.1-fold was observed. Urinary recovery of unchanged PF-07081532 was low, with less than 0.2% of the dose recovered in the 24-hour dosing interval following last dose administration. Interparticipant variability for PF-07081532 exposure ranged from 17% to 51% CV for C_{max} and 15% to 62% CV for AUC_{tau} across all doses. No substantial differences in PF-07081532 exposure (C_{max} and AUC_{tau}) were observed between participants with T2DM and obesity either after single dose (Day 1, 10 mg) or multiple dose (Day 28, 120 mg and Day 42, 180 mg) administration.

In Study C3991003 following single-dose (Day 1) and multiple-dose (Day 42) administration of PF-07081532, peak plasma PF-07081532 concentrations (C_{max}) were observed at 1 to 2 hours and 2 to 5 hours, respectively. Terminal $t_{½}$ averaged 24.37 to 26.04 hours following multiple-dose administration (Day 42). PF-07081532 exposure (C_{max} and AUC_{tau}) increased in an approximately dose-proportional manner across the dose range studied. Accumulation with QD dosing was less than 2-fold. No substantial differences were observed in the achieved exposures (both C_{max} and AUC_{tau}) between participants with T2DM and obesity either after single-dose (Day 1, 20 mg) or multiple-dose (Day 42, 60 mg) administration.

Refer to the IB for more details on the clinical PK of PF-07081532.

2.3. Benefit/Risk Assessment

PF-07081532 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and pharmacokinetic data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07081532 may be found in the IB, which is the SRSD for this study. The SRSD for the site sourced itraconazole and cyclosporine capsule products are the corresponding USPIs.[13,14]

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: PF-07081532		
Thyroid C-cell tumors	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, dulaglutide, semaglutide, 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. Of note, similar tumors were not seen in rodent studies with PF-07081532, likely as PF-07081532 does not stimulate rodent GLP-1 receptors.	Potential participants with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 are excluded from the clinical development program. Thyroid function tests are included in the clinical trial protocols to monitor participants' thyroid function.
Pancreatitis	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide, semaglutide and dulaglutide). One SAE of obstructive pancreatitis has been observed in the PF-07081532 clinical trial program, which was considered to be treatment-related by the investigator, but unrelated by the sponsor.	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 clinical studies.
Hypoglycemia	Clinical trials with injectable GLP-1R agonists have not demonstrated an increased risk for hypoglycemia. But 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. A low overall frequency of generally mild hypoglycemia has been reported in the PF-07081532 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 during the study. Participants are informed about the signs and symptoms of hypoglycemia and are monitored for these symptoms during the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Impairment in renal function	Potential risks are based on product labeling for injectable GLP-1R agonists, and predominantly occur in patients with significant nausea, vomiting, and dehydration. In the clinical trial program only one mild adverse event (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 by lab assessments of serum urea, creatinine and eGFR. Hydration will be encouraged, and reduced fluid intake and evidence of dehydration, if detected, will be treated by close clinical follow-up.
Gastrointestinal adverse reactions	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide, semaglutide and dulaglutide). Gastrointestinal AEs, the majority of which were mild in severity, have been observed in the clinical program with PF-07081532. In nonclinical studies with PF-07081532, gastrointestinal adverse effects were observed in rats and monkeys.	Participants are monitored during the clinical studies to prevent potential sequelae of any severe gastrointestinal reactions, eg, dehydration. Hydration will be encouraged and concomitant medication for nausea is permitted in the study.
Diabetic retinopathy complications	The potential risk is based on the product labeling for the injectable GLP-1R agonist semaglutide and dulaglutide in patients with T2DM. There are no nonclinical or clinical data involving PF-07081532 to suggest an increased risk of diabetic retinopathy complications.	Potential participants with diabetes mellitus are excluded from this clinical study.
Suicidal ideation and behavior	The potential risk is based on the product labeling for the injectable GLP-1R agonists liraglutide and semaglutide for obesity based on long-term studies. Suicidal ideation has not been observed in the PF-07081532 clinical studies to date.	Suicidal ideation and behavior, along with symptoms of depression, will be monitored at specified intervals during the study using the C-SSRS and PHQ-9 questionnaires, with referral to a MHP for further evaluation if needed.
Changes in heart rate	Potential risk is based on the product labeling for the injectable GLP-1R agonists, liraglutide and semaglutide, for T2DM and obesity. Modest increases in HR have been noted in the early clinical studies with PF-07081532, with most values remaining within the normal range.	HR is monitored during the clinical study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Declines in body weight	Decreased appetite and body weight loss have been reported for marketed GLP-1R agonists and declines in body weight have been noted at higher doses of PF-07081532.	Weight is collected at multiple timepoints and will be monitored throughout the trial.
Acute gallbladder disease	Potential risk is based on the product labeling for the injectable GLP-1R agonists, semaglutide and liraglutide, for T2DM and obesity. Acute gallbladder disease has not been observed in the PF-07081532 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: Itraconazole		
Rare cases of serious hepatotoxicity, including liver failure and death. There have been reports of congestive heart failure. In post-marketing experience, heart failure was more frequently reported in patients receiving a total daily dose of 400 mg although there were also cases reported among those receiving lower total daily doses. Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole.	Risk based on product labeling.	Multiple oral doses of 200 mg QD for 9 days are administered in this study and pose minimal risk. Participants will be monitored in an inpatient clinical research unit.
Study Intervention: Cyclosporine		
Systemic hypertension, hepatotoxicity and nephrotoxicity; the risk increases with increasing dose and duration of cyclosporine therapy. Renal dysfunction, including structural kidney damage, is a potential consequence of cyclosporine, and therefore, renal function must be monitored during therapy.	Risk based on product labeling.	A single oral dose of 600 mg is administered in the study and poses minimal risk. Participants will be monitored in an inpatient clinical research unit. Hydration will be encouraged and concomitant medication for nausea is permitted in the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
Risk of COVID-19 exposure during study	Study participants could be infected with the SARS-CoV-2 virus during study participation. This could lead to increased health risk for this participant and others in the study.	Participants undergo COVID-19 specific assessments at admission to study site and when symptoms arise.

2.3.2. Benefit Assessment

While PF-07081532 is not expected to provide any significant long-term clinical benefit to the healthy, overweight or obese participants in this relatively short-term study, potential benefits may include weight loss, receiving medical evaluations/assessments associated with clinical study visits (eg, physical examinations, ECGs, labs), and contributing to the process of developing a potential new therapy for T2DM and obesity.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07081532 may be found in the IB, which is SRSD, for this study.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with PF-07081532 are justified by the anticipated benefits that may be afforded to participants who are overweight or obese.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effect of MD itraconazole on the single-dose PK of PF-07081532 in otherwise healthy, overweight or obese participants.	• PF-07081532 PK parameter: AUC_{inf} (if data permit[a] otherwise AUC_{last})
• To estimate the effect of SD cyclosporine on the single-dose PK of PF-07081532 in otherwise healthy, overweight or obese participants.	• PF-07081532 PK parameter: AUC_{inf} (if data permit[a] otherwise AUC_{last})
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-07081532 administered separately and in combination with itraconazole or cyclosporine in otherwise healthy, overweight or obese participants.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To evaluate the effects of itraconazole or cyclosporine on additional PK parameters for PF-07081532.	• Additional plasma PK parameters for PF-07081532: C_{max} and T_{max}; and CL/F, V_z/F, $t_{½}$, as data permit.

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

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, fixed-sequence, 3-period study to evaluate the effect of multiple doses of itraconazole and a single dose of cyclosporine on the single-dose PK of PF-07081532 in otherwise healthy, overweight or obese adult participants. The 3 study periods will be conducted consecutively without a break.

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 Period 1 Day 1. Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and sponsor.

Approximately 16 participants will be enrolled in the study such that approximately 12 evaluable participants complete the study.

The total duration of participation from the Screening Visit to the F/U telephone contact will be approximately 82 days or 12 weeks, approximately 3 weeks of which will be conducted on an inpatient basis. The 21-day inpatient portion of the study will be conducted as follows:

Period 1: Days -1 to 5 (Study Days -1 to 5; participants are admitted to the CRU on Day -1), 40 mg SD PF-07081532 on Day 1;

Period 2: Days 1 to 5 (Study Days 6 to 10), 40 mg SD PF-07081532 plus 600 mg SD cyclosporine on Day 1;

Period 3: Days 1 to 10 (Study Days 11 to 20; participants are discharged from the CRU on Study Day 20), 200 mg itraconazole QD ×9 days plus 40 mg SD PF-07081532 on Day 4.

A telephone F/U contact will occur 28-35 days from the last dose of study intervention (Period 3, Day 9).

4.2. Scientific Rationale for Study Design

The purpose of this study is to characterize the effect of multiple doses of itraconazole and a single dose of cyclosporine on the SD PK of PF-07081532 in otherwise healthy, overweight or obese adult participants.

In vitro data indicate that PF-07081532 is a substrate for the hepatic uptake transporter, OATP1B3. Likewise, an increase in the plasma AUC exposure of PF-07081532 was observed during coadministration of an OATP inhibitor in monkeys. Therefore, a single dose of cyclosporine will be coadministered with PF-07081532 in this study to assess the impact of an OATP inhibitor on the single-dose PK of PF-07081532.

In vitro data also indicate that CYP3A is the predominant CYP isoform contributing to the metabolism of PF-07081532. Therefore, multiple doses of itraconazole will be co-administered with PF-07081532 in this study to assess the impact of a CYP3A strong inhibitor on the single-dose PK of PF-07081532.

PF-07081532 will be administered as a single 40 mg dose in all 3 study periods, and all dosing will be administered with food in order to minimize gastrointestinal related AEs.

Participants will include overweight or obese males and females to represent the target population. Additionally, WOCBP will be permitted with the stipulation that they comply with the contraceptive guidelines provided in Appendix 4.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for PF-07081532, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

The 40 mg dose of PF-07081532 has been chosen based on safety and tolerability considerations during co-administration of either a CYP3A or OATP inhibitor. Because PF-07081532 was shown to be an OATP substrate in vitro, and because co-administration of an OATP inhibitor with PF-07081532 in monkeys resulted in a notable increase in PF-07081532 plasma AUC exposure, a conservative dose of 40 mg has been chosen in the event cyclosporine co-administration results in significant increases in PF-07081532 exposure (refer to Section 2.2.2).

Itraconazole is considered to be a strong inhibitor of CYP3A.[15] The 200 mg QD itraconazole dosing regimen (3-day lead-in) has been chosen based on recommendations provided by the Innovation and Quality in Pharmaceutical Development's Clinical Pharmacology Leadership Group[16] and is expected to provide adequate inhibition of CYP3A. Multiple DDI studies using 100–200 mg/day of itraconazole with a 3-day lead-in have demonstrated that adequately strong CYP3A inhibition is observed with this strategy.[17,18,19] Following the co-administration of itraconazole and PF-07081532 on Day 4 of Period 3, itraconazole administration will continue for an additional 5 days in order to maintain inhibition of CYP3A throughout the PK sampling duration of PF-07081532.

Itraconazole is available as either capsules or solution for oral administration and either may be used when conducting DDI studies.[16] The oral solution formulation will be administered in the current study as it provides higher systemic exposures, has less PK variability, and offers greater flexibility with respect to dosing (fed or fasted) compared to the capsule formulation.[20,21] Finally, a total duration of 2 weeks of itraconazole dosing is a reasonable limit for minimizing unnecessary itraconazole exposure and potential safety risks associated with longer exposure,[16] therefore, the 9-day dosing duration planned for the current study is expected to be safe and well-tolerated.

Cyclosporine is an FDA recommended inhibitor of OATP.[15] The 600 mg single dose of cyclosporine has been chosen based on previous experience in clinical DDI studies and is expected to provide maximal inhibition of OATP, with adequate safety and tolerability.[22,23]

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit or the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreening tool is utilized for study recruitment purposes; it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, and race, and ethnicity. 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. Otherwise healthy female and male participants must be at least 18 years of age at the time of signing the ICD (healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, physical examination, including blood pressure and pulse rate measurement, standard 12-lead ECG and clinical laboratory tests).

    - Women can be of child-bearing potential, but cannot be pregnant, breastfeeding, or planning to become pregnant while participating in the study, may not be taking either oral contraceptives or non-oral hormonal contraceptives (with the exception of implantable progestogen only or intrauterine hormone releasing system), and must avoid vaccination within live attenuated vaccines. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Other Inclusion Criteria:

2. BMI: ≥25.0 kg/m^2 at Screening.

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

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

5. Capable of giving signed informed consent as described in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations, 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).

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

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

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

    - Known hypersensitivity to itraconazole or cyclosporine.

2. 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.

3. 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). Anyone with any history of pancreatic CA will be excluded, even if it was resected and they were considered 'cured'.

4. Personal or family history of MTC or MEN2, or study participants with suspected MTC per the investigator's judgment.

5. Acute pancreatitis, history of repeated episodes of acute pancreatitis, or history of chronic pancreatitis.

6. Symptomatic gallbladder disease.

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

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

9. Known medical history of active liver disease, including chronic hepatitis B or C, primary biliary cirrhosis, alcoholic liver disease, primary sclerosing cholangitis, autoimmune hepatitis, overlap syndrome, or prior known drug-induced liver injury.

10. History of HIV infection.

11. Any lifetime history of a suicide attempt.

Prior/Concomitant Therapy

12. 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 6.9 for additional details).

13. Use of any medications that are:

    - Moderate or strong CYP3A4/5 and/or CYP2C19 inhibitors within 14 days or 5 half-lives (whichever is longer),

    - Moderate or strong CYP3A and/or CYP2C19 inducers within 14 days or 5 half-lives (whichever is longer),

    - Systemic therapy with inhibitors of OATP transporters within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention (Refer to Section 6.9 for additional details).

14. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s) (Refer to Section 6.9 for additional details).

15. Any vaccine (eg, COVID/influenza) within 7 days prior to the first dose of study intervention.

Prior/Concurrent Clinical Study Experience:

16. Previous administration with a GLP-1R agonist (other than PF-07081532) within 90 days preceding the first dose of study intervention used in this study. Previous

administration with PF-07081532 within 30 days preceding the first dose of study intervention used in this study.

17. Previous administration with an investigational product (drug or vaccine) 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).

Diagnostic Assessments (at Screening unless otherwise indicated)

18. A PHQ-9 score ≥15 obtained at Screening or Day -1 in Study.

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

20. A positive urine drug test.

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

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

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

23. 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 level ≥1.25 × ULN.

    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

- TSH >1.5x ULN or <LLN.
- Serum calcitonin >ULN.
- Amylase or lipase >ULN.
- Fasting blood glucose ≥126 mg/dL.
- Fasting C-peptide not within normal limit.
- eGFR <75 mL/min/1.73 m^2 as calculated by the CKD-EPI equation.

24. Positive testing for HIV, HBsAg, HBcAb, 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. Anyone who has a history of HBV that is treated/cleared is excluded. Hepatitis B vaccination is allowed.

25. A positive SARS-CoV-2 test.

Other Exclusions: at Screening unless indicated

26. 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).

27. Current use of tobacco or nicotine containing products in excess of the equivalent of 5 cigarettes per day.

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

29. History of sensitivity to heparin or heparin induced thrombocytopenia.

30. Unwilling or unable to comply with the criteria or procedures in the study.

31. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their 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, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample. The predose PK sample should be taken prior to consumption of the breakfast meal on Day 1 in Periods 1 and 2, and on Day 4 in Period 3.

- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- During CRU confinement, participants should begin consumption of a standard breakfast (morning) approximately 30 minutes prior to dosing. The breakfast meal will be consumed over approximately a 20-minute period, with the study intervention administered within approximately 10 minutes of completion of the meal. Participants will be encouraged to consume the entire meal.

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after 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 14 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.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample.

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.4. 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 (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

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 on the CRF.

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and auxiliary medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to PF-07081532, itraconazole, and cyclosporine.

6.1. Study Intervention(s) Administered

Study Intervention(s)			
Intervention Name	PF-07081532	Itraconazole	Cyclosporine
Arm Name (group of participants receiving a specific treatment or no treatment)	All participants	All participants	All participants
Type	Drug	Drug	Drug
Dose Formulation	Tablet	Solution	Capsule
Unit Dose Strength(s)	20 mg	10 mg/mL	100 mg
Dosage Level(s)	40 mg	200 mg (20 mL)	600 mg (6 × 100 mg)
Route of Administration	Oral	Oral	Oral
Use	Substrate	Perpetrator	Perpetrator
IMP or AxMP	IMP	AxMP	AxMP
Sourcing	Provided centrally by the sponsor	Provided locally by the trial site	Provided locally by the trial site
Packaging and Labeling	Study intervention will be supplied by Pfizer to the CRU in bulk along with individual dosing containers, as necessary, for unit dosing.	Commercially available itraconazole will be supplied by the CRU.	Commercially available cyclosporine will be supplied by the CRU.
[Current/Former Name(s) or Alias(es)]	N/A	SPORANOX®	NEORAL®

Study Arm(s)			
Arm Title	Period 1: PF-07081532	Period 2: Cyclosporine + PF-07081532	Period 3: Itraconazole + PF-07081532
Arm Type	No intervention	Experimental (DDI)	Experimental (DDI)
Arm Description	Participants will receive PF-07081532 as a single 40 mg dose on Day 1.	Participants will receive a single 40 mg dose of PF-07081532 and a single 600 mg dose of cyclosporine on Day 1.	Participants will receive itraconazole 200 mg QD × 9 days plus a single 40 mg dose of PF-07081532 on Day 4.

Study Arm(s)			
Associated Intervention Labels	20 mg PF-07081532 oral tablets	20 mg PF-07081532 oral tablets; Commercially available cyclosporine 100 mg capsules	20 mg PF-07081532 oral tablets; Commercially available itraconazole solution (10 mg/mL)

PF-07081532 20 mg oral tablets will be provided by Pfizer to the CRU in bulk along with individual dosing containers, as necessary, for unit dosing.

Commercially available itraconazole will be supplied by the CRU.

Commercially available cyclosporine will be supplied by the CRU.

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive study intervention with the breakfast meal at approximately 0800 hours (±2 hours). Investigator site personnel will administer PF-07081532, itraconazole, or cyclosporine during each period (as applicable per SoA) with ambient temperature water to a total volume of approximately 240 mL. On coadministration day, participants may receive additional ambient temperature water up to 100 mL, if needed. Details regarding meals on dosing days are provided in Section 5.3.2.

Participants will swallow the study intervention whole and will not manipulate or chew (as relevant) the study intervention prior to swallowing.

PF-07081532 must be administered within approximately 10 minutes of completion of the morning meal. PF-07081532 will be administered first and itraconazole or cyclosporine will be administered within 5 minutes of PF-07081532 during the DDI assessment periods.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. 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 upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, 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 excursion definition and information to report for each excursion will be provided to the site in the PCRU local/site procedures.

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

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff 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.

8. Further guidance and information for the final disposition of unused study interventions are provided in the PCRU's local/site procedures. 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.

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/capsules/solution 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, capsules, or solution will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Assignment to Study Intervention

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. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Blinding

This is an open label study.

6.5. 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. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.6. Dose Modification

Dose modification will not be permitted in this study for any study intervention.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

For this study, any dose of PF-07081532 greater than 1.6 g within a 24-hour time period will be considered an overdose. A single dose of 1.6 g is projected to result in exposure that will exceed that observed at the NOAEL in the pivotal 9-month toxicology study in monkeys, after accounting for species differences in plasma protein binding.

For this study, overdose for itraconazole or cyclosporine will be as per the USPI labels.[13,14]

There is no specific treatment for an overdose of PF-07081532. Treatment of overdose should consist of general supportive measures.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer 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 study 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 study medical monitor as needed based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

Study participants will abstain from all concomitant treatments, except for the treatment of AEs, as described in the Exclusion Criteria section 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.

Sytemic therapy with moderate or strong CYP3A4/5 and/or CYP2C19 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention are prohibited. Systemic therapy with inhibitors of OATP transporters within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention are prohibited.

Use of a GLP-1R agonist is prohibited within 90 days prior to the first dose of study intervention, with the exception of PF-07081532, which is prohibited within 30 days prior to the first dose of study drug.

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.

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

Implantable progestogen or intrauterine hormone releasing system only are allowed to be used in participants who are WOCBP (see Appendix 4).

Females using hormonal contraceptives that do not meet the requirements of this study or who are 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.

6.9.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07081532; standard medical supportive care must be provided to manage the AEs, including administration of carbohydrates to treat HAEs (see Section 8.3.6).

6.9.1.1. Management of Nausea and Vomiting

Nausea and vomiting have been reported with administration of GLP-1R agonists and also with administration of PF-07081532 (see Section 2.2.4). Study participants complaining of nausea may be managed conservatively with bed rest and/or fluid management at the discretion of the investigator. If 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.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent 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 8.3.8, should be discontinued from dosing at investigator discretion.

- Positive SARS-CoV-2 Test.

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 permanently discontinued, the participant should remain in the study to be evaluated for safety. 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, post-treatment study follow-up, and/or future collection of additional information.

7.1.1. Potential Cases of Acute Kidney Injury

Abnormal values in Scr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in Scr level relative to the participant's own baseline measurement should trigger another assessment of Scr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in Scr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal Scr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating Scr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the

abnormal Scr. If ≥2 healthy participants in a given period are noted to have 2 *consecutive* Scr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following: safety, behavioral, compliance, administrative reasons, and/or if the study is terminated by the sponsor.

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

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

The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant withdraws from the study, they 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 will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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 them 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 the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative 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.

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, eg, retained research samples, 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 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 they have 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 200 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

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

8.2. Efficacy Assessments

Efficacy is not evaluated in this study.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

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

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

light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.4.1 to Section 8.4.3.

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

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. If triplicate measurements are obtained, they should be collected approximately 2 minutes apart.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.4.1 to Section 8.4.3.

8.3.2.2. Temperature

Temperature will be measured orally at Screening. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA of this protocol using an ECG methodology that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs,

then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria 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 QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. 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 significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that 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 significant and abnormal during participation in the study or within 28 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 study 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 DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

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.

8.3.5. COVID-19 Specific Assessments

Participants will be tested for COVID-19 infection by PCR at admission to the clinic for confinement, and if they develop COVID-19 -like symptoms. Additional testing may be required by local regulations or by the PI.

8.3.6. Management of Hypoglycemia

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

Any episode of hypoglycemia must be captured on the HAE CRF with specific details captured on the HAE Form CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.3.6.1 below.

For medical management of hypoglycemia, the investigator may administer oral carbohydrate, glucagon, or IV glucose according to his or her medical judgment.

8.3.6.1. Definition and Severity of Categorization of Hypoglycemic Adverse Event

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

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

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

b. Documented symptomatic hypoglycemia: An event during which typical symptoms of HAE are accompanied with a glucose value of <70 mg/dL (3.9 mmol/L), using glucometer at the study site or sponsor identified central/local laboratory, and the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or IV glucose.

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

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

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

2. The participant exhibited at least 1 of the following neurological symptoms:

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

3. Either:

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

8.3.6.2. 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.

8.3.7. Pregnancy Testing

A serum pregnancy test is required at Screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study prior to discharge on Period 3 Day 10. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3.8. Suicidal Ideation and Behavior Risk Monitoring

8.3.8.1. Columbia Suicide Severity Rating Scale

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior.[25] The "baseline/screening" version of the C-SSRS[26] 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[27] 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.

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

The PHQ9-9 is a 9 item self-report scale for the assessment of depressive symptoms.[28] 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 or Day -1 indicates clinically significant depression and serves as an exclusion criterion for this study (see Section 5.2).

8.3.8.3. 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 suicidal behavioral question on the C-SSRS.
- A score of ≥10 on the PHQ-9.
- In the investigator's judgment a risk assessment or exclusion is required.

A clinically qualified MHP is an 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.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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).

During the active collection period as described in Section 8.4.1, 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.

8.4.1. 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 undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues 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 permanently 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 information on AEs or SAEs 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 they consider 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.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 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 its being available.

8.4.1.2. 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 8.4.1, 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.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

8.4.2. 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.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or 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 provided in Appendix 3.

8.4.4. 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 toward 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.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental

exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. 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 inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion then inseminates 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/participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a followup to the initial EDP Supplemental Form. In the case of a live birth, the structural

integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- 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.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

The investigator must report EDB 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 EDB 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 EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the occupational exposure 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 must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. 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.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	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.

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.

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

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

8.5. Pharmacokinetics

Blood samples of approximately 3 mL, to provide approximately 1 mL of plasma, will be collected for measurement of plasma concentrations of PF-07081532 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing.

Samples will be used to evaluate the PK of PF-07081532. Each plasma sample will be divided into 2 aliquots (1 each for primary and backup). Samples collected for analyses of PF-07081532 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal CCI purposes.

Genetic analyses will not be perfo1med on these plasma samples.

Samples collected for measurement of plasma concentrations of PF-07081532 will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or explorato1y methods.

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

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 infonned of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

CCI [redacted]

8.7. Biomarkers

Biomarkers are not evaluated in this study.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summaiy and statistical analyses of the data collected in this study is outlined here and further detailed in the 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 primaiy endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypothesis

No fonnal statistical hypothesis testing will be perfonned in this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a paiticipant's, or their legally authorized representative's, agreement to paiticipate in a clinical study following completion of the info1med consent process and assignment to study intervention. A paiticipant will be considered enrolled if the info1med consent is not withdrawn prior to paiticipating in any study activity after screening. Potential paiticipants who ai·e screened for the pmpose of dete1mining eligibility for the study, but do not paiticipate in the study, are not considered enrolled, unless othe1wise specified by the protocol.

Participant Analysis Set	Description
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK concentration set	All participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported.
PK parameter set	All participants who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of primary interest are reported.

9.3. 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.

9.3.1. Pharmacokinetic Analyses

9.3.1.1. Derivation of Pharmacokinetic Parameters

Plasma PK parameters of PF-07081532 will be derived (as data permits) from the concentration-time data using standard noncompartmental methods as outlined in Table 4. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 4. Plasma PK Parameters for PF-07081532

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
AUC_{inf}[a]	Area under the plasma concentration-time profile from time zero extrapolated to infinite time.	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum plasma concentration.	Observed directly from data.
T_{max}	Time for C_{max}.	Observed directly from data as time of first occurrence.

Table 4. Plasma PK Parameters for PF-07081532

Parameter	Definition	Method of Determination
$t_{½}$[a]	Terminal half-life.	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F[a]	Apparent oral clearance.	$Dose/AUC_{inf}$.
V_z/F	Apparent volume of distribution.	$Dose/ (AUC_{inf} \bullet k_{el})$.

a. as data permit

9.3.1.2. Statistical Methods for PK Data

Natural log_e transformed AUC_{inf} of PF-07081532 administered without cyclosporine or coadministered with cyclosporine 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% CIs will be obtained from the models. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. The test treatment will be 'PF-07081532 40 mg singe dose and cyclosporine' (Period 2), which will be reported separately in comparison to the reference treatment of 'PF-07081532 40 mg singe dose without cyclosporine' (Period 1).

Natural log_e transformed AUC_{inf} of PF-07081532 administered without itraconazole or coadministered with itraconazole 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% CIs will be obtained from the models. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. The test treatment will be 'PF-07081532 40 mg singe dose and itraconazole' (Period 3), which will be reported separately in comparison to the reference treatment of 'PF-07081532 40 mg singe dose without itraconazole' (Period 1).

PK parameters, including plasma AUC_{inf}, AUC_{last}, C_{max}, T_{max}, and CL/F, V_z/F, $t_{½}$, as data permit, of PF-07081532 will be summarized descriptively by treatment. For AUC_{inf}, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for AUC_{inf} will be plotted by treatment.

The plasma concentrations of PF-07081532 will be listed and descriptively summarized by nominal PK sampling time and treatment. Individual participant, as well as mean and median profiles, of the plasma concentration-time data will be plotted by treatment using actual (for individual) and nominal (for mean and median) times, respectively. Mean and median profiles will be presented on both linear and semi-log scales.

Additional specifications regarding the tables, listings, and figures will be outlined in the SAP.

9.3.2. Safety Analyses

All safety analyses will be perfo1med on the safety population.

AEs, ECGs, BP, pulse rate, body weight, and safety laborato1y data will be reviewed and summarized on an ongoing basis dming the study to evaluate the safety of paiiicipants. Body weight will be summarized descriptively by period. Any clinical laborato1y, ECG, BP, and pulse rate abnonnalities of potential clinical concern will be described. Safety data will be presented in tabulai·and/or graphical fo1mat and smnmai·ized descriptively, where appropriate.

Medical histo1y and physical exainination and neurological examination infonnation, as applicable, collected during the course of the study, will be considered source data and will not be required to be repo1ied, unless othe1wise noted. However, any untowai·d 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 ai·e used for inclusion/exclusion criteria, such as laborato1y data, ECGs, and vital signs, will be considered source data, and will not be required to be repo1ied, unless othe1wise noted. Demographic data collected at screening will be repo1ied.

9.3.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG pai·ameters HR, QTcF, PR interval, and QRS complex will be summarized by period and time. The frequency of uncoITected QT values above 500 ms will be tabulated.

The number (%) of pa1iicipants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by period:

Safety QTcF Assessment

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

Baseline will be pre-dose on Day I.

9.3.2.2. Mental Health

Assessment of mental health as dete1mined by C-SSRS and PHQ-9. Details will be provided in the SAP.

CCI [redacted]

9.4. Interim Analyses

No 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 and PK assessments.

9.5. Sample Size Determination

Approximately 16 participants will be enrolled in the study such that approximately 12 evaluable participants complete the study.

A sample size of 12 participants will provide adequate precision to estimate the relative bioavailability of PF-07081532. The following table presents the width of 90% CI for different estimated effects, with 80% coverage probability.

Parameter	Estimated Effect (100*Test/Reference)	90% CI		CI Width
AUC_{inf}	85%	66.46%	108.71%	42.25%
	90%	70.37%	115.11%	44.74%
	95%	74.28%	121.50%	47.22%
	100%	78.19%	127.90%	49.71%
	105%	82.10%	134.29%	52.20%
	110%	86.01%	140.69%	54.68%
	115%	89.92%	147.08%	57.17%

These estimates are based on the assumption that within-participant standard deviation is 0.291 for $lnAUC_{inf}$ as obtained from study C3991001.

Participants who withdraw from the study or discontinue treatment, or whose PK samples are considered to be non-evaluable with respect to the primary PK objective may be replaced at the discretion of the investigator upon consultation with the sponsor. For participants who remain in the study, the SAP will address PK data associated with episodes of vomiting following administration of study intervention and/or missed doses for any of the study interventions.

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, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, 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 the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Informed Consent Process

The investigator or the investigator'srepresentative will explain the nature of the study, including the risks and benefits, 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, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each 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 their 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 theirmedical 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 theirright to access and correct theirpersonal data and to withdraw consent for the processing of theirpersonal 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 on which 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 IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

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

10.1.3. 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 their actual identity and medical record ID. 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.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.4. Committees Structure

10.1.4.1. Data Monitoring Committee

This study will not use an E-DMC.

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/CTIS, and/or www.pfizer.com, and other public registries and websites 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/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-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 data from these trials available 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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, including definition of study-critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and IQMP maintained and utilized by the sponsor or designee.

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

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.

In this study, the CRF will serve as the source document. 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.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor or sponsor's designee (Pfizer CRU).

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor or sponsor's designee (Pfizer CRU).

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

The sponsor or designee will perform mornitoring 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 guidelines, and all applicable regulatory requirements.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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 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 the ICH 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

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer 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-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.10. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, and (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant.

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 5. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and creatinine Cystatin C and eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT TBili Alkaline phosphatase Uric acid Albumin Total protein	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[a]	• Urine drug screening[b] • Pregnancy test (β-hCG)[c] • COVID-19 testing At Screening: • FSH[d] • HIV, HbsAg, HCVAb, HbcAb, HCV RNA[e] • HbA1C • TSH • Calcitonin • C-peptide • Amylase and lipase
	Required: For suspected DILI: AST/ALT TBili, direct and indirect bili Total bile acids, GGT Total protein, albumin CK PT, INR Acetaminophen/paracetamol or protein adduct levels Hepatitis serology (even if screening negative)		

a. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
b. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
c. Serum or urine β-hCG for female participants of childbearing potential.
d. For confirmation of postmenopausal status only.
e. The test will be performed if HCV is positive.

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.

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 occmTence in a patient or clinical study paiiicipant, 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 abno1mal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

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

- Any abno1mal laborato1y test results (hematology, clinical chemistiy, 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 abnonnal laborato1y 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 medicaVsurgical intervention;
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustinents) or discontinuation from the study, significant additional conc01nitant drng ti·eatinent, or other therapy.
- Exacerbation of a chronic or inte1mittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administl'ation, even though it may have been present before the staii of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drng-drng 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 repo1ied as an AE or SAE unless it is an intentional overdose taken with possible suicidaVself-haiming intent. Such overdoses should be repo1ied regardless of sequelae.

Events Meeting the AE Definition
• Any clinically significant abno1mal laborato1y findings or other abno1mal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the paiiicipant'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 paiiicipant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untowai·d medical occmTence 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 staii of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is **life-threatening** The te1m "life-threatening" in the definition of "serious" refers to an event in which the paiiicipant 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 admitted (usually involving at least an overnight stay) at the hospital or emergency wai·d 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" occmTed or was necessaiy, 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 or significant disability/incapacity

- The te1m disability means a substantial dismption of a person's ability to conduct nonnal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diaiThea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent eve1yday life functions but do not constitute a substantial dismption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic

The event may be suspected from clinical symptoms or laborato1y findings indicating an infection in a pa1ticipant exposed to a Pfizer product. The tenns "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by phaimacovigilance personnel. Such cases ai·e also considered for repo1ting as product defects, if appropriate.

g. **Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE repo1ting is appropriate in other situations, such as significant medical events that may jeopai·dize the paiticipant 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 diug dependency or diug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for repo1ting SAEs on the CT SAE Repo1t Fo1m to Pfizer Safety throughout the active collection period. 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	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or 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 or 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 or 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 paiiicipant 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 info1mation. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE repo1ied during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfo1i, but poses no significant or pennanent risk of haim to the research paiiicipant.

- Severe: A type of AE that intenupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

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 occmTence of each AE or SAE. The investigator will use clinical judgment to dete1mine the relationship.

- 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 rnled out.

- Alternative causes, such as underlying disease(s), concoinitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention adininistration, will be considered and investigated.

- The investigator will also consult the IB and/or product info1mation, for mai·keted products, in their assessment.

- For each AE or SAE, the investigator !!!!!.U document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occmTed and the investigator has minimal info1mation to include in the initial repo1i 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 theiropinion of causality in light of follow-up info1mation and send an SAE follow-up repo1i with the updated causality assessment.
- The causality assessment is one of the criteria used when dete1mining regulato1y repo1iing 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 repo1iing pmposes, as defined by the sponsor. In addition, if the investigator dete1mines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and repo1i such an assessment in the dedicated section of the CT SAE Repo1i Fo1m and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perfonn or aiTange 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 laborato1y tests or investigations, histopathological exaininations, or consultation with other healthcai·e providers.
- If a paiiicipant dies during paiiicipation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmo1iem findings, including histopathology.
- New or updated infonnation will be recorded in the originally submitted documents.
- The investigator will subinit any updated SAE data to the sponsor within 24 hours of receipt of the info1mation.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primaiy mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to repo1t the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper f01m (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entiy of new data or changes to existing data.
- If a site receives a report of a new SAE from a study paiticipant or receives updated data on a previously repo1ted SAE after the electi·onic DCT has been taken off-line, then the site can repo1t this infonnation on a paper SAE f01m (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Repo1t Fo1m is the prefeITed method to ti·ansmit this infonnation to Pfizer Safety.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transpo1t Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Repo1t Fo1m 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 Repo1t Fo1m pages within the designated repo1ting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

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 definition in Section 10.4.3).

  OR

- Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier method of contraception. 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 a 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.

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.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

2. Intrauterine device.

3. Intrauterine hormone releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

6. 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.

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[redacted]

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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 T bili for suspected Hy's law cases, 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, or 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, 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 T bili 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: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to estimate glomerular filtration rate [Scr-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline serum Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations[29]

2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.[29]

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
1. Marked sinus bradycardia (rate <40 bpm) lasting minutes. 1. New PR interval prolongation >280 ms. 2. New prolongation of QTcF to >480 ms (absolute) or by60 ms from baseline. 3. New-onset atrial flutter or fibrillation, with controlled venti·icular response rate: ie, rate <120 bpm. 4. New-onset type I second-degree (Wenckebach) AV block of>30 seconds' duration. 5. Frequent PVCs, triplets, or sho1i inte1vals (<30 seconds) of consecutive venti·icular complexes.
ECG Findings That <u>May</u> Qualify as SAEs
6. QTcF prolongation >500 ms. 7. New ST-T changes suggestive of myocardial ischemia. 8. New-onset LBBB (QRS complex>120 ms). 9. New-onset right bundle branch block (QRS complex>120 ms). 10. Symptomatic bradycardia. 11. Asystole: • In awake, symptom-free paiiicipants in sinus rhythm, with documented periods of asystole3 . 0seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node. • In awake, symptom-free paiiicipants with atrial fibrillation and bradycai·dia with 1 or more pauses of at least 5 seconds or longer. • Atrial flutter or fibrillation, with rapid venti·icular response rate: rapid = rate >120 bpm. 12. Sustained supraventriculai·tachycai·dia (rate>120 bpm) ("sustained"= short duration with relevant symptoms or lasting>1 minute). 13. Ventriculai·rhythms >30 seconds' duration, including idioventi·icular rhythm (HR <40 bpm), accelerated idioventriculai·rhythm *(HR* >40 bpm to <100 bpm), and

monomo1phic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).

14. Type II second-degree (Mobitz II) AV block.

15. Complete (third-degree) heait block.

ECG Findings That Qualify as SAEs

16. Change in pattern suggestive of new myocai·dial infai·ction.

17. Sustained ventriculai·tachyaiThythmias (>30 seconds' duration).

18. Second- or third-degree AV block requiring pacemaker placement.

19. Asystolic pauses requiring pacemaker placement.

20. Atrial flutter or fibrillation with rapid ventriculai·response requiring cardioversion.

21. Ventriculai·fibrillation/flutter.

22. At the discretion of the investigator, any aiThythmia classified as an adverse expenence.

The enumerated list of major events of potential clinical concem 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 repo1ted as AEs/SAEs.

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AM	before noon
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{tau}	area under the plasma concentration-time profile over the dosing interval, tau
AUC_{24}	area under the plasma concentration-time profile from time zero to time 24 hours
AV	atrioventricular
AxMP	auxiliary medicinal products
β-hCG	beta human chorionic gonadotropin
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	clearance
CL/F	apparent oral clearance
C_{last}	predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
CL_p	plasma clearance
C_{max}	maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial

Abbreviation	Term
CTIS	Clinical Trials Information System
CTMS	Clinical Trial Management System
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
EC	ethics committee
ECC	Emergency Contact Card
eCrCl	estimated creatinine clearance
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EE	ethinyl estradiol
eGFR	estimated glomerular filtration rate
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
EV	extracellular vesicles
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide 1
GLP-1R	glucagon-like peptide 1 receptor
HAE	hypoglycemic adverse event
HbA1c	hemoglobin A_{1c}
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IL	Interleukin
IMP	investigational medicinal product

Abbreviation	Term
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IQMP	Integrated Quality Management Plan
IRB	Institutional Review Board
IV	intravenous(ly)
KDIGO	Kidney Disease: Improving Global Outcomes
k_{el}	first-order elimination rate constant
LBBB	left bundle branch block
LE	levonorgestrel
LFT	liver function test
LLN	Lower limit of normal
MD	multiple dose
MEN2	multiple endocrine neoplasia syndrome type 2
MHP	mental health professional
MQI	medically qualified individual
MTC	medullary thyroid carcinoma
NA	not applicable
NOAEL	no observed adverse effect level
OATP	organic anion transporting polypeptides
PCR	polymerase chain reaction
PCRU	Pfizer Clinical Research Unit
PE	physical examination
pH	potential of hydrogen
PHQ-9	Patient Health Questionnaire-9
PI	principal investigator
PK	pharmacokinetic(s)
PR	pulse rate
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
QTL	quality tolerance limits
RA	rheumatoid arthritis
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C

Abbreviation	Term
SD	single dose; standard deviation
SIB	Suicidal Ideation and Behavior
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
ST-T	ST segment to T wave changes on 12-lead ECG
SSID	study-specific subject identification number
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal elimination half-life
T2DM	type 2 diabetes mellitus
T4	thyroxine
TBA	total bile acids
TBili	total bilirubin
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to C_{max}
TNF-α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
UA	urine analysis
UGT	uridine 5'-diphospho glucuronosyltransferase
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
UTI	urinary tract infection
V_{ss}	volume of distribution at steady state
Vz/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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