**Title Page**

# A PHASE 1, OPEN-LABEL, 2-PERIOD, 2-SEQUENCE, CROSSOVER STUDY TO COMPARE THE SINGLE-DOSE PHARMACOKINETICS OF 2 DIFFERENT FORMULATIONS OF PF-07081532 ADMINISTERED ORALLY TO ADULT PARTICIPANTS WHO ARE OVERWEIGHT OR OBESE

| | |
|---|---|
| **Study Intervention Number:** | PF-07081532 |
| **Study Intervention Name:** | Not Applicable |
| **US IND Number:** | CCI |
| **EudraCT/EU CT Number:** | Not Applicable |
| **ClinicalTrials.gov ID:** | Not Available |
| **Pediatric Investigational Plan Number:** | Not Applicable |
| **Protocol Number:** | C3991010 |
| **Phase:** | 1 |

**Brief Title:** Phase 1 Study to Compare PK of Single Oral Doses of 2 Different PF-07081532 Formulations in Adult Participants Who Are Overweight or Obese



[redacted]

## Document History

| Document | Version Date |
|---|---|
| Original protocol | 30 November 2022 |

**TABLE OF CONTENTS**



[redacted]

[redacted]

## LIST OF TABLES

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Protocol Title:** A Phase 1, Open-Label, 2-Period, 2-Sequence, Crossover Study to Compare the Single-Dose Pharmacokinetics of 2 Different Formulations of PF-07081532 Administered Orally to Adult Participants Who Are Overweight or Obese

**Brief Title:** Phase 1 Study to Compare PK of Single Oral Doses of 2 Different PF-07081532 Formulations in Adult Participants Who Are Overweight or Obese

### Regulatory Agency Identification Number(s):

| | |
|---|---|
| **US IND Number:** | CCI |
| **EudraCT/EU CT Number:** | Not Applicable |
| **ClinicalTrials.gov ID:** | Not Available |
| **Pediatric Investigational Plan Number:** | Not Applicable |
| **Protocol Number:** | C3991010 |
| **Phase:** | 1 |

### Rationale:

The purpose of the study is to evaluate the relative bioavailability following oral administration of 2 formulations of PF-07081532. In Periods 1 and 2, the PK of the formulation projected to be used in future clinical studies (PF-07081532 80 mg immediate release tablet, Formulation B) will be compared with the PK of the current formulation (PF-07081532 20 mg immediate release tablet + 60 mg immediate release tablet, Formulation A) in the fasted state in adult participants who are overweight or obese.

### Objectives and Endpoints:

| Objectives | Endpoints |
|---|---|
| **Primary:** | **Primary:** |
| • To compare the relative bioavailability of PF-07081532 following administration of a single oral dose of Formulation B (Test) compared to Formulation A (Reference) administered in the fasted state to adult participants who are overweight or obese. | • Plasma: PF-07081532 $AUC_{inf}$ (as data permit, otherwise $AUC_{last}$) and $C_{max}$ for Formulations A and B. |
| **Secondary:** | **Secondary:** |
| • To evaluate the safety and tolerability of a single oral dose of PF-07081532 administered in the fasted state to adult participants who are overweight or obese. | • Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters. |

**Overall Design:**

This is a randomized, open-label, single dose, 2-period, 2-sequence, crossover study. Participants will be screened for participation in this study within 28 days before dosing in Period 1 to confirm that they meet the inclusion/exclusion criteria for this study. A minimum of 6 days between the single 80 mg doses (80 mg immediate release tablet for Formulation B, 20 mg immediate release tablet + 60 mg immediate release tablet for Formulation A) administered in each period will be employed. The expected duration of participation from Screening to the Follow-up telephone contact will be approximately 10 weeks.

**Number of Participants:**

Approximately 20 participants will be enrolled to ensure at least 14 evaluable participants with PK data.

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 randomization/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:**

Inclusion and exclusion criteria are listed below:

**Inclusion Criteria**

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

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

2. Male and female participants who are healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vitals and ECGs.

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

4. A total body weight >50 kg (110 lb) and BMI of 25.0 to <34.9 $kg/m^2$, inclusive, at the screening visit.

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

**Exclusion Criteria**

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

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, ileal resection).

    - History of HIV infection, hepatitis B, or hepatitis C; positive testing at screening for HBsAg, HBcAb, HCVAb or HIV. Hepatitis B vaccination is allowed.

2. Personal or family history of MTC or MEN2 or pancreatitis, or participants with suspected MTC per the investigator's judgement.

3. 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.

4. 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.

5. In females, current use of hormone replacement therapy or oral/injectable contraceptives containing ethinyl estradiol.

6. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives (whichever is longer) preceding the first dose of study intervention used in this study. Investigational products which are strong CYP3A inducers or time-dependent inhibitors are prohibited within 14 days plus 5 half-lives or 30 days (whichever is longer) prior to the dose of study intervention.

7. Known prior participation (ie, randomized and received at least 1 dose of investigational product) in a study involving PF-07081532 or known intolerance to a GLP-1R agonist.

8. A positive urine drug test.

9. Using a properly sized and calibrated BP cuff, screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) the BP should be repeated 2 more

times and the average of the 3 BP values should be used to determine the participant's eligibility.

10. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second or third degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If 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.

11. 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:

    - 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;
    - HbA1c ≥6.5%;
    - Fasting blood glucose ≥126 mg/dL (7 mmol/L);
    - Calcitonin > ULN;
    - eGFR <60 mL/min/1.73 $m^2$ as calculated by the CKD-EPI equation.

12. 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).

13. Participants with current use of tobacco and/or nicotine containing products exceeding equivalent of 5 cigarettes per day.

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

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

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

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

**Study Arms and Duration:**

| **Study Intervention(s)** | | |
|---|---|---|
| **Intervention Name** | PF-07081532 | |
| **Arm Name (group of participants receiving a specific treatment or no treatment)** | Sequence 1 | Sequence 2 |
| **Unit Dose Strength(s)** | 20 mg<br>60 mg<br>80 mg | |
| **Route of Administration** | Oral | |
| **Use** | Experimental | |
| **IMP or NIMP/AxMP** | IMP | |

| **Study Arm(s)** | | |
|---|---|---|
| **Arm Title** | Sequence 1 | Sequence 2 |
| **Arm Type** | Experimental | Experimental |
| **Arm Description** | Participants will receive a single dose of PF-07081532 20 mg immediate release tablet + 60 mg immediate release tablet (Formulation A) on Period 1 Day 1, and receive a single dose of PF-07081532 80 mg immediate release tablet (Formulation B) on Period 2 Day 1, with a minimum of 6 days between 2 doses. | Participants will receive a single dose of PF-07081532 80 mg immediate release tablet (Formulation B) on Period 1 Day 1, and receive a single dose of PF-07081532 20 mg immediate release tablet + 60 mg immediate release tablet (Formulation A) on Period 2 Day 1, with a minimum of 6 days between 2 doses. |

**Statistical Methods:**

A sample size of 14 participants will provide adequate precision to estimate the relative bioavailability of PF-07081532.

**PK parameters:**

Plasma PK parameters of PF-07081532 will be derived (as data permit) from the concentration-time data using standard noncompartmental methods. 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.

Natural log transformed $AUC_{inf}$ (if data permit), $AUC_{last}$ and $C_{max}$ will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within the sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Formulation A (PF-07081532 20 mg + 60 mg) will be the Reference treatment while Formulation B (PF-07081532 80 mg) will be the Test treatment.

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

**Safety:**

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

**Ethical Considerations:**

A single dose of PF-07081532 is not expected to provide any clinical benefit to study participants. Results from this study will be used to evaluate the effect of formulation on the relative bioavailability of PF-07081532.

### 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 information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

**SoA-Table 1. Study Schedule of Assessment**

| **Visit Identifier** Abbreviations used in this table may be found in Appendix 10. | **Screening** | **Periods 1 and 2** | | | | | | **ET** | **Follow -Up** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **Day -28 to Day -2** | **Day -1 (Period 1 Only)** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | | **28-35 days** | • All screening should be done ≤28 days before the first dose.<br>• Day relative to start of study intervention (Day 1).<br>• Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention. |
| **Hours After Dose** | | | **0** | | **48** | **72** | **96** | | | |
| Informed consent | X | | | | | | | | | |
| Demography | X | | | | | | | | | |
| COVID-19 assessment | See Notes | | | | | | | | | • Assessment of risk for, symptoms of or testing for COVID-19 may be performed at admission to the CRU and/or at other times during the study at investigator discretion and according to local site policies. |
| Review of eligibility criteria | X | X | | | | | | | | |
| Inpatient stay at Clinical Research Unit | | X | → | → | → | → | X | | | |
| Medical history | X | X | | | | | | | | |

## SoA-Table 1. Study Schedule of Assessment

| **Visit Identifier** Abbreviations used in this table may be found in Appendix 10. | **Screening** | **Periods 1 and 2** | | | | | | **ET** | **Follow -Up** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **Day -28 to Day -2** | **Day -1 (Period 1 Only)** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | | **28-35 days** | • All screening should be done ≤28 days before the first dose.<br>• Day relative to start of study intervention (Day 1).<br>• Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention. |
| **Hours After Dose** | | | **0** | | **48** | **72** | **96** | | | |
| Physical exam | X | X | | | | | | X | | • At screening: height & body weight only.<br>• Complete PE at Day -1 of Period 1; otherwise brief physical exam for findings during previous PE or new/open AEs at PI discretion. |
| Contraception use (females only) | X | X | | | | | | X | X | • WOCBP only |
| Prior/concomitant treatments | X | X | | | | | | X | X | |
| Single, supine 12-lead ECG | X | | X | | | | X | X | | • Day 1 ECG: to be conducted pre-dose<br>• Day 5 ECG: in Period 2 only. |
| Single, supine vital sign assessment (BP and pulse rate) | X | | X | | | | X | X | | • Day 1 assessment: to be conducted pre-dose<br>• Day 5 assessment: in Period 2 only. |
| Serious and non-serious adverse event monitoring | X | X | → | → | → | → | X | X | X | |
| Study intervention administration | | | X | | | | | | | • Following ≥10-hr fast; and for Period 2, a minimum 6-day interval from dosing in the previous period. |
| Urine drug test | X | X | | | | | | | | |
| Urinalysis (and microscopy, if needed) | X | X | | | | | X | X | | • Day 5: Procedures at discharge (Period 2) only. |

[redacted]

## SoA-Table 1. Study Schedule of Assessment

| Visit Identifier<br>Abbreviations used in this table may be found in Appendix 10. | Screening | Periods 1 and 2 | | | | | | ET | Follow-Up | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **Day -28 to Day -2** | **Day -1 (Period 1 Only)** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | | **28-35 days** | • All screening should be done ≤28 days before the first dose.<br>• Day relative to start of study intervention (Day 1).<br>• Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention. |
| **Hours After Dose** | | | **0** | | **48** | **72** | **96** | | | |
| **Blood samples for:** | | | | | | | | | | |
| Clinical laboratory tests after 4-hour fast | X | X | | | | | X | X | | • See Appendix 2 for details of clinical laboratory tests<br>• Day 5: Procedures at discharge (Period 2) only. |
| FSH (postmenopausal females only), HBsAg, HBcAb, HCVAb, calcitonin | X | | | | | | | | | |
| HIV | X | | | | | | | | | |
| Pregnancy test (WOCBP only) | X | X | | | | | X | X | | • Day 5: Procedures at discharge (Period 2) only. |
| CCI [redacted] | | | [redacted] | | | | | | | [redacted] |
| CCI [redacted] | | | [redacted] | | | | | | | [redacted] |

[redacted]

## SoA-Table 2. Schedule of PK Sampling

| Visit Identifier | Periods 1 and 2 | | | | | | | | | | | | | | | | ET | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day | 1 | | | | | | | | | | | 2 | | 3 | 4 | 5 | | |
| Hours Before/After Dose | 0 | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 10 | 12 | 16 | 24 | 36 | 48 | 72 | 96 | - | Hour 0 = predose sample collection |
| Study intervention administration | X | | | | | | | | | | | | | | | | | Following ≥10-hr fast; and for Period 2, a minimum 6-day interval from dosing in the previous period. |
| 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-1 receptor (GLP-1R) stimulates insulin release, inhibits glucagon secretion in a glucose-dependent manner, and delays gastric emptying.[2,3] In addition, GLP-1 has been shown to increase satiety and suppress food intake.[4]

PF-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

The purpose of the study is to evaluate the relative bioavailability following oral administration of 2 formulations of PF-07081532. In Periods 1 and 2, the PK of the formulation projected to be used in future clinical studies (PF-07081532 80 mg immediate release tablet, Formulation B) will be compared with the PK of the current formulation (PF-07081532 20 mg immediate release tablet + 60 mg immediate release tablet, Formulation A) in the fasted state in adult participants who are overweight or obese.

## 2.2. Background

### 2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology program are included in the IB.

CCI

[redacted]

### 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.

[redacted]

CCI

[redacted]

Further details of the nonclinical toxicology program are included in the IB.

### 2.2.4. Clinical Overview

Two clinical studies (C3991001 and C3991002) have been completed with PF-07081532 in which a total of 88 participants have been randomized. Across these 2 studies, 22 healthy adult participants, 51 adult participants with T2DM, and 15 adult participants with obesity have been randomized, with a total of 74 unique participants exposed to at least 1 dose of PF-07081532.

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.

#### 2.2.4.1. Clinical Safety

The safety profile of PF-07081532 has been assessed in 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 up to 42 days has been considered safe, with a tolerability profile consistent with the MoA. The majority of TEAEs have been mild in intensity and in the Gastrointestinal Disorders SOC.

Following single dose administration to healthy adult participants in study C3991001, the most frequently reported all-causality TEAEs across all treatment groups were nausea and vomiting, with an increased incidence of GI AEs noted at the dose of 200 mg. In the multiple ascending dose study, C3991002, the most frequently reported all-causality TEAEs included

[redacted]

nausea in participants with T2DM, and nausea and constipation in participants with obesity. Higher incidences of GI TEAEs were observed in the higher dose groups of PF-07081532 (120 mg and 180 mg QD) compared to placebo. There were no clinically significant adverse trends in safety laboratory tests, vital signs, or ECG parameters in either study with increasing PF-07081532 doses.

Refer to the IB for more detail on these studies, and the known drug class effects of marketed GLP-1R agonists.

CCI

[redacted]

### 2.3. Benefit/Risk Assessment

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.

[redacted]

### 2.3.1. Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention(s) PF-07081532** | | |
| Gastrointestinal adverse reactions | The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide, semaglutide and dulaglutide).<br>In addition, GI AEs, the majority of which were mild in severity, have been observed in the clinical program with PF-07081532. | The single dose and dose level administered in this study minimize any potential risk. |
| Hypoglycemia | Clinical trials with injectable GLP-1R agonists have not demonstrated an increased risk for hypoglycemia. However, when administered in combination with anti-diabetic agents that are known to have an increased risk of hypoglycemia (such as insulin or sulfonylureas), an increased risk for hypoglycemia was observed. | The single dose and dose level administered in this study minimize any potential risk. The participants enrolled will not have diabetes and will not be receiving anti-diabetic agents. Study includes inpatient monitoring of the participants following administration of a single dose of the study intervention. |
| Increased heart rate | Based on the product labeling for the injectable GLP-1R agonist liraglutide for obesity, mean increases in resting heart rate ranged 2 to 3 bpm in clinical trials, with some participants experiencing greater increases in resting heart rate, up to 10-20 bpm.<br>Following single dose administration of PF-07081532 in the completed FIH study, variable increases in heart rate were observed; the majority of individual values remained within normal ranges, and, throughout the study, no AEs or clinical symptoms related to vital sign parameters were reported. | The single dose and dose level administered in this study minimize any potential risk.<br>Study includes inpatient monitoring of the participants following administration of a single dose of the IP. |
| Other potential risks associated with long-term dosing of marketed GLP-1R agonists include thyroid C-cell tumors, pancreatitis, impairment in renal function, diabetic retinopathy complications, | These potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, dulaglutide, exenatide and | The single dose and dose level administered in this study minimize any potential risk. |

[redacted]

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| suicidal ideation/behavior and acute gallbladder disease | semaglutide); additional information is provided in the IB. | Study includes inpatient monitoring of the participants following administration of a single dose of the IP.<br><br>Participants with a personal or family history of MTC or MEN2; with acute pancreatitis or a history of chronic pancreatitis are not eligible for study entry. |
| **Other** | | |
| Risk of COVID-19 exposure during study | During the pandemic, study participants could be exposed to the SARS-CoV-2 virus during study participation. This could lead to increased health risk for this participant and others in the study. | Assessment of risk for, symptoms of or testing for COVID-19 may be performed at admission to the CRU and/or at other times during the study at investigator discretion and according to local site policies. |

### 2.3.2. Benefit Assessment

Participation in this study is not expected to benefit study participants, but the results of this study will inform the effect of formulation on the pharmacokinetics of PF-07081532 and formulation to be taken forward into Phase 2/3 studies.

### 2.3.3. Overall Benefit/Risk Conclusion

Based on the profile of PF-07081532 observed in nonclinical and clinical studies to date and taking into account the measures to minimize risk to study participants, the potential risks identified in association with study intervention are justified and supports continued clinical development of PF-07081532.

## 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary:** | **Primary:** |
| • To compare the relative bioavailability of PF-07081532 following administration of a single oral dose of Formulation B (Test) compared to Formulation A (Reference) administered in the fasted state to adult participants who are overweight or obese. | • Plasma: PF-07081532 $AUC_{inf}$ (as data permit, otherwise $AUC_{last}$) and $C_{max}$ for Formulations A and B. |
| **Secondary:** | **Secondary:** |
| • To evaluate the safety and tolerability of a single oral dose of PF-07081532 administered in the fasted state to adult participants who are overweight or obese. | • Assessment of treatment emergent AEs, clinical laboratory abnormalities, vital signs, ECG parameters. |
| **Other:** | **Other:** |
| • To determine additional pharmacokinetic parameters of PF-07081532 following administration of a single oral dose of PF-07081532 as Formulation A (Reference) and Formulation B (Test) in the fasted state to adult participants who are overweight or obese. | • Additional plasma PK parameters:<br>  • $AUC_{last}$<br>  • CL/F and $V_z$/F , as data permit<br>  • $T_{max}$<br>  • Half-life ($t_{½}$), as data permit. |

## 4. STUDY DESIGN

### 4.1. Overall Design

This is a randomized, open-label, single dose, 2-period, 2-sequence, crossover study. Participants will be screened for participation in this study within 28 days before dosing in Period 1 to confirm that they meet the inclusion/exclusion criteria for this study. A minimum washout of 6 days between the single 80 mg doses (80 mg immediate release tablet for Formulation B, 20 mg immediate release tablet + 60 mg immediate release tablet for Formulation A) administered in each period will be employed. The expected duration of participation from Screening to the Follow-up telephone contact will be approximately 10 weeks.

Approximately 20 participants will be enrolled to ensure at least 14 evaluable participants with PK data.

**Table 3. Randomization Schedule**

| | Period 1 | Period 2 |
|---|---|---|
| Sequence 1 (N=10) | Formulation A | Formulation B |
| Sequence 2 (N=10) | Formulation B | Formulation A |

Formulation A (Reference) will be administered as PF-07081532 20 mg immediate release tablet + 60 mg immediate release tablet, and Formulation B (Test) will be administered as a PF-07081532 80 mg immediate release tablet.

### 4.2. Scientific Rationale for Study Design

The Phase 2 clinical development program for PF-07081532 uses cold-storage immediate release tablets (Formulation A). A different, room temperature storage, immediate release formulation (Formulation B) is planned to be used in future clinical studies. Since the primary comparison of formulations in this study is between Formulations A and B, these formulations will be assessed in a cross-over manner in this study. These results will aid in identification of an equivalent dose to Formulation A for subsequent clinical studies where Formulation B is expected to be used. Consistent with the regulatory guidance, a single-dose design will be used in this study because these are generally more sensitive than steady-state studies in assessing the rate and extent of release of the drug substance from the drug product into the systemic circulation.[5,6]

The results from the assessment of the effect of food on exposure indicate that PF-07081532 may be administered without regard to food (refer to IB). Inter-participant variability for PF-07081532 exposure after administration with food based on geometric %CV ranged from 12% to 29% for $C_{max}$ and 28% to 34% for $AUC_{inf}$, and was comparable to the variability observed under fasted conditions. Thus, PF-07081532 will be administered in the fasted state, which is also consistent with the recommendation in the regulatory guidance for studies assessing relative bioavailability.

CCI [redacted]

#### 4.2.1. Choice of Contraception/Barrier Requirements

Both women of childbearing potential, as well as those who are of non-childbearing potential, may be enrolled given the availability of EFD toxicity studies with PF-07081532.

[redacted]

However, measures will be taken to limit the risk of pregnancy in the female population enrolled (see SoA and Section 10.4).

To limit potential for interaction and confounding effects on PK, participants taking hormone replacement therapy or oral/injectable contraceptives containing ethinyl estradiol are excluded from this study.[7]

The potential risk of exposure to PF-07081532 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[8]

#### 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

A single oral dose of 80 mg will be used in this study. This dose has been selected based on prior experience in clinical studies with PF-07081532 (Section 2.2.4).

In Study C3991001, a single dose of 30 mg was very well tolerated with an AE profile that did not differ from placebo. In the same study, single ascending doses up to 200 mg were tested and were considered safe and had a tolerability profile in line with expectations for the MoA, with the majority of AEs being mild in severity and in the GI SOC (with nausea and vomiting the most frequently observed). For participants that experienced vomiting (observed at the 100 and 200 mg dose levels, with increased frequency at 200 mg), this generally occurred after the attainment of $C_{max}$ and with no apparent impact on PF-07081532 exposure. The dose proposed in the current study (80 mg) reflects adequate safety margins compared to nonclinical toxicity studies.

Although doses greater than 80 mg QD will be evaluated in future clinical trials, 80 mg was chosen for this study because it is expected to result in acceptable gastrointestinal tolerability allowing for a robust assessment of pharmacokinetics and is within the clinically relevant dose range being assessed in Phase 2 studies. CCI [redacted]

### 4.4. End of Study Definition

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

[redacted]

A participant is considered to have completed the study if he/she had completed both Periods of the study, including the follow-up visit via telephone contact 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. Male and female participants must be at least 18 years of age, inclusive, at the time of signing the ICD.

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

**Type of Participant and Disease Characteristics:**

2. Male and female participants who are healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs and ECGs.

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

**Weight:**

4. A total body weight >50 kg (110 lb) and BMI of 25.0 to <34.9 kg/$m^2$, inclusive, at the screening visit.

**Informed Consent:**

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

## 5.2. Exclusion Criteria

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

**Medical Conditions:**

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

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

    - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

2. Personal or family history of MTC or MEN2 or pancreatitis, or participants with suspected MTC per the investigator's judgement.

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

**Prior/Concomitant Therapy:**

4. 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 and Appendix 9 for additional details).

5. In females, current use of hormone replacement therapy or oral/injectable contraceptives containing ethinyl estradiol.

**Prior/Concurrent Clinical Study Experience:**

6. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives (whichever is longer) preceding the first dose of study intervention used in this study. Investigational products which are strong CYP3A inducers or time-dependent inhibitors are prohibited within 14 days plus 5 half-lives or 30 days (whichever is longer) prior to the dose of study intervention.

7. Known prior participation (ie, randomized and received at least 1 dose of investigational product) in a study involving PF-07081532 or known intolerance to a GLP-1R agonist.

**Diagnostic Assessments:**

8. A positive urine drug test.

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

10. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

11. 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:

    - 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;
    - HbA1c ≥6.5%;
    - Fasting blood glucose ≥126 mg/dL (7 mmol/L);
    - Calcitonin > ULN;
    - eGFR <60 mL/min/1.73 $m^2$ as calculated by the CKD-EPI equation.

**Other Exclusion Criteria:**

12. 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).

[redacted]

13. Participants with current use of tobacco and/or nicotine containing products exceeding equivalent of 5 cigarettes per day.

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

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

16. 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.

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

### 5.3. Lifestyle Considerations

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

#### 5.3.1. 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 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 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.

- 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.

- 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 of each study period.
- 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 of each study period.
- 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 ***not*** be permitted to engage in physically strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests while participating in the study; physical activity at an individual participant's normal pace is 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) and eating 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 at the joint discretion of the investigator and medical monitor.

[redacted]

# 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational 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.

## 6.1. Study Intervention(s) Administered

| Study Intervention(s) | | |
|---|---|---|
| **Intervention Name** | PF-07081532 | |
| **Arm Name (group of participants receiving a specific treatment or no treatment)** | Sequence 1 | Sequence 2 |
| **Type** | Drug | |
| **Dose Formulation** | Tablet | |
| **Unit Dose Strength(s)** | 20 mg, 60 mg, 80 mg | |
| **Dosage Level(s)** | 80 mg, single dose (refer to **Arm Description** below) | |
| **Route of Administration** | Oral | |
| **Use** | Experimental | |
| **IMP or NIMP/AxMP** | IMP | |
| **Sourcing** | Provided centrally by the sponsor. | |
| **Packaging and Labeling** | Study intervention will be provided as open-label supply in bulk bottles along with individual dose containers, as necessary, for unit dosing. | |
| **Current/Former Name(s) or Alias(es)** | PF-07081532 20 mg immediate release tablet +<br>PF-07081532 60 mg immediate release tablet (Formulation A);<br>PF-07081532 80 mg immediate release tablet (Formulation B). | |

| Study Arm(s) | | |
|---|---|---|
| **Arm Title** | Sequence 1 | Sequence 2 |
| **Arm Type** | Experimental | Experimental |
| **Arm Description** | Participants will receive a single dose of PF-07081532 20 mg immediate release tablet + 60 mg immediate release tablet (Formulation A) on Period 1 Day 1, and receive a single dose of PF-07081532 80 mg immediate release tablet (Formulation B) on Period 2 Day 1, with a minimum of 6 days between 2 doses. | Participants will receive a single dose of PF-07081532 80 mg immediate release tablet (Formulation B) on Period 1 Day 1, and receive a single dose of PF-07081532 20 mg immediate release tablet + 60 mg immediate release tablet (Formulation A) on Period 2 Day 1, with a minimum of 6 days between 2 doses. |
| **Associated Intervention Labels** | PF-07081532 | |

Tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

### 6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours) on Day 1 of Periods 1 and 2. Investigator site personnel will administer study intervention during each period with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

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

## 6.3. 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.

### 6.4.1. Blinding of Participants

Participants will be unblinded to their assigned study intervention.

### 6.4.2. Blinding of Site Personnel

Investigators and other site staff will be unblinded to participants' assigned study intervention.

### 6.4.3. Blinding of the Sponsor

Sponsor staff will be unblinded to participants' assigned study intervention.

## 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.

A record of the number of study intervention tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

## 6.6. Dose Modification

Dose modification of PF-07081532 is not allowed.

## 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.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician 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 3 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

### 6.9. Prior and Concomitant Therapy

Use of any prescription or non-prescription 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 or **as outlined in Section 10.9**. Participants will abstain from all concomitant treatments during the study, except for the treatment of AEs. Limited use of non-prescription medications that are not believed to affect participant safety or the overall results of the study **may be permitted on a case-by-case basis following approval by the sponsor** and as long as they are not listed in Section 10.9. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Females using hormonal injectable or oral contraceptives or taking hormone replacement therapy containing ethinyl estradiol 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.

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 AEs observed with PF-07081532; standard medical supportive care must be provided to manage any AEs.

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Intervention

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

## 7.2. Participant Discontinuation/Withdrawal From the Study

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

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

The early 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.

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

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

The total blood sampling volume for individual participants in this study is approximately 130 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 Concomitant Therapy sections of the protocol.

### 8.2. Efficacy Assessments

Not applicable.

### 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 as per the SoA and recorded in the CRF. 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 Sections 8.4.1 to 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.

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 Sections 8.4.1 to 8.4.3.

### 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 section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 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 within the respective period. 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 5 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or 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

Assessment of risk for, symptoms of, or testing for COVID-19 may be performed at admission to the CRU, and/or at other times during the study at investigator discretion and according to local site policies.

### 8.3.6. 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. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

## 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 (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, except as indicated below, 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 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 theyconsider 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.

[redacted]

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

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

- Spontaneous abortion including miscarriage and missed abortion 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 plasma, will be collected into appropriately labeled tubes containing $K_2$EDTA 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. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples will be used to evaluate the PK of PF-07081532. Each plasma sample will be divided into 2 aliquots (1 for measurement and 1 for 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, CCI

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

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

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

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

CCI

CCI [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 summary 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 primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

### 9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

### 9.2. Analysis Sets

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

| Participant Analysis Set | Description |
|---|---|
| Enrolled/Randomly assigned to study intervention | "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are |

| Participant Analysis Set | Description |
|---|---|
| | 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. |
| Safety Analysis Set | All participants 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 interest are reported. Should vomiting occur after administration of PF-07081532, the resulting PK parameters from that participant from the corresponding period may be excluded, where further details will be provided in the SAP. |

## 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

Participants who experience events that may affect their PK profile (such as vomiting) may be excluded from the PK analysis. Evaluability criteria will be further specified in the SAP.

Plasma PK parameters of PF-07081532 will be derived (as data permit) 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**

| Parameter | Definition | Method of Determination |
|---|---|---|
| $AUC_{inf}$[a] | Area under the concentration-time curve from time zero extrapolated to infinity | $AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis |
| $AUC_{last}$ | Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration ($C_{last}$). | Linear/Log trapezoidal method. |

**Table 4. Plasma PK Parameters**

| Parameter | Definition | Method of Determination |
|---|---|---|
| $C_{max}$ | Maximum observed concentration | Observed directly from data |
| $T_{max}$ | Time for $C_{max}$ | Observed directly from data as time of first occurrence |
| $t_{½}$[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 loglinear 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 clearance | $Dose/AUC_{inf}$ |
| $V_z/F$[a] | Apparent volume of distribution | $Dose/(AUC_{inf} \times k_{el})$ |

a. If data permit.

Natural log transformed $AUC_{inf}$ (if data permit), $AUC_{last}$ and $C_{max}$ will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within the sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Formulation A (PF-07081532 20 mg + 60 mg) will be the Reference treatment while Formulation B (PF-07081532 80 mg) will be the Test treatment.

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

### 9.3.2. Safety Analyses

All safety analyses will be performed on the safety population.

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

Medical history and PE and neurological examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical

and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

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

### 9.4. Interim Analyses

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

### 9.5. Sample Size Determination

A sample size of 14 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 | 85% | 67.87% | 106.45% | 38.58% |
| | 90% | 71.86% | 112.71% | 40.85% |
| | 95% | 75.86% | 118.97% | 43.12% |
| | 100% | 79.85% | 125.23% | 45.39% |
| | 105% | 83.84% | 131.5% | 47.65% |
| | 110% | 87.83% | 137.76% | 49.92% |
| | 115% | 91.83% | 144.02% | 52.19% |
| $C_{max}$ | 85% | 74.47% | 97.02% | 22.54% |
| | 90% | 78.85% | 102.72% | 23.87% |
| | 95% | 83.23% | 108.43% | 25.20% |
| | 100% | 87.61% | 114.14% | 26.52% |
| | 105% | 91.99% | 119.84% | 27.85% |
| | 110% | 96.38% | 125.55% | 29.18% |
| | 115% | 100.76% | 131.26% | 30.50% |

These estimates are based on the assumption that within-participant standard deviations are 0.291 and 0.171 for $\ln AUC_{inf}$ and $\ln C_{max}$, respectively, 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.

# 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's representative 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 their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about 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

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

#### 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.

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 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'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'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/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or 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 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, (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 Laboratory Assessment**

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hemoglobin<br>Hematocrit<br>RBC count<br>MCV<br>MCH<br>MCHC<br>Platelet count<br>WBC count<br>Total neutrophils (Abs)<br>Eosinophils (Abs)<br>Monocytes (Abs)<br>Basophils (Abs)<br>Lymphocytes (Abs) | BUN<br>Creatinine (Scr)<br>Cystatin C (Scys)<br>Glucose (fasting)<br>Calcium<br>Sodium<br>Potassium<br>Chloride<br>Total $CO_2$ (Bicarbonate)<br>AST<br>ALT<br>Alkaline phosphatase<br>Total bilirubin<br>Creatine kinase[a]<br>Uric acid<br>Albumin<br>Total protein<br>eGFR[b]<br>HbA1C[c] | pH<br>Glucose (qual)<br>Protein (qual)<br>Blood (qual)<br>Ketones<br>Nitrites<br>Leukocyte esterase<br>Urobilinogen<br>Urine bilirubin<br><br>Microscopy[d] | COVID-19 test[e]<br>Urine drug test[f]<br><br>Serum pregnancy test[g]<br><br>**At screening only:**<br>• Serum FSH[h]<br>• Serology[i]: HBsAg, HBcAb, HCVAb, HIV<br>• Calcitonin<br><br>***For suspected DILI:***<br>AST/ALT<br>Total bilirubin, direct and indirect bilirubin<br>Alkaline phosphatase<br>Total bile acids, GGT<br>Total protein, albumin<br>CK<br>PT, INR<br>Acetaminophen/paracetamol or protein adduct levels<br>Hepatitis serology (even if screening negative)<br><br>***For suspected DICI/DIKI:***<br>Creatinine (SCr)<br>Cystatin C (SCys)[j]<br>eGFR (SCr only and combined SCr+SCys)[j]<br><br>Spot (dipstick) UACR |

a. At screening and Day -1.
b. eGFR should be calculated using the 2021 CKD-EPI Scr only equations; see Appendix 7.
c. At screening only.
d. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.

[redacted]

**Table 5. Protocol Required Laboratory Assessment**

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|

e. Assessment of risk for, symptoms of or testing for COVID-19 may be performed at admission to the CRU and/or at other times during the study at investigator discretion and according to local site policies.
f. Minimum testing requirements include cocaine, THC, opiates and opioids, benzodiazepines and amphetamines.
g. Serum β-hCG in WOCBP only.
h. In postmenopausal females only.
i. HBsAb will be tested if HBsAg and/or HBcAb is positive.
j. For suspected DICI/DIKI, reflex measurement of Scys will be conducted and eGFR will be calculated using both the 2021 CKD-EPI Scr only and the 2021 CKD-EPI Scr-Scys Combined equations, see Appendix 7.
For a list of abbreviations, refer to Appendix 10.

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.

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

[redacted]

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

### 10.3.1. Definition of AE

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

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

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

### 10.3.2. Definition of 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**<br><br>The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br><br>In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.<br><br>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 term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**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 laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

**g. Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 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 reporting SAEs on the CT SAE Report Form 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.

[redacted]

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<br><br>**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)*<br>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 participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

**Assessment of Intensity**

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

- Mild: 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 discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts 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 occurrence of each AE or SAE. The investigator will use clinical judgment to determine 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 ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** 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 occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.
- The investigator may change theiropinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

**Follow-Up of AEs and SAEs**

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

[redacted]

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

### 10.3.4. Reporting of SAEs

**SAE Reporting to Pfizer Safety via an Electronic DCT**

- The primary 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 report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (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 entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

**SAE Reporting to Pfizer Safety via the CT SAE Report Form**

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport 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 Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

## 10.4. Appendix 4: Contraceptive 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.

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

### 10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

<u>Highly Effective Methods That Have Low User Dependency</u>

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.

Highly Effective Methods That Are User Dependent

6. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral + barrier*
   - Injectable + barrier*

Sexual Abstinence

7. 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

* Acceptable barrier methods to be used concomitantly with options 6 for the study include any of the following:

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

CCI

## 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

| **2021 CKD-EPI Scr Only**[9] | **Scr** *(mg/dL)* | **Scys** *(mg/L)* | **Recommended eGFR Equation** |
|---|---|---|---|
| Female | if ≤ 0.7 | N/A | $eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$ |
| Female | if > 0.7 | N/A | $eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$ |
| Male | if ≤ 0.9 | N/A | $eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$ |
| Male | if > 0.9 | N/A | $eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$ |
| **2021 CKD-EPI Scr-Scys Combined**[9] | **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.

## 10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

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

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

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

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

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

**ECG Findings That Qualify as SAEs**

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

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

## 10.9. Appendix 9: Prohibited Concomitant Medications

The prohibited concomitant medications listed below should not be taken with PF-07081532 for the period of time at least equal to the required washout period listed in the table, and throughout the conduct of the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

| Drug Category | Drugs (Therapeutic Class) | Washout Period Requirement Prior to the First Dose of Study Intervention |
|---|---|---|
| **CYP3A Inhibitor (strong)** | Boceprevir (Antiviral),<br>Ceritinib (Kinase Inhibitor),<br>Clarithromycin (Antibiotic),<br>Cobicistat (Pharmacokinetic Enhancer),<br>Conivaptan (Diuretic),<br>Danoprevir and Ritonavir (Antiviral),<br>Elvitegravir and Ritonavir (Treatment of AIDS),<br>Grapefruit juice (Food Product),<br>Idelalisib (Kinase Inhibitor),<br>Indinavir (Protease Inhibitor),<br>Indinavir and Ritonavir (Protease Inhibitor),<br>Itraconazole (Antifungal),<br>Josamycin (Antibiotic)<br>Ketoconazole (Antifungal),<br>LCL161 (Cancer Treatment),<br>Lonafarnib (Misc agent; Rare diseases)<br>Lopinavir and Ritonavir (Protease Inhibitor),<br>Mibefradil (Calcium Channel Blocker),<br>Mifepristone (Antiprogestin),<br>Nefazodone (Antidepressant),<br>Nelfinavir (Protease Inhibitor),<br>Nirmatrelvir + Ritonavir (Protease Inhibitor),<br>Posaconazole (Antifungal),<br>Ribociclib (Kinase Inhibitor), | 14 days or 5 half-lives, whichever is longer |

| Drug Category | Drugs (Therapeutic Class) | Washout Period Requirement Prior to the First Dose of Study Intervention |
|---|---|---|
| | Ritonavir (Protease Inhibitor),<br>Saquinavir (Protease Inhibitor),<br>Saquinavir and Ritonavir (Protease Inhibitor),<br>Telaprevir (Antiviral),<br>Telithromycin (Antibiotic),<br>Tipranavir and Ritonavir (Protease Inhibitor),<br>Troleandomycin (Antibiotic),<br>Tucatinib (Kinase Inhibitor),<br>Ombitasvir and Paritaprevir and Ritonavir and Dasabuvir (Antiviral),<br>Voriconazole (Antifungal) | |
| **CYP3A Inducer (strong)** | Apalutamide (Antiandrogen),<br>Avasimibe (Antilipemic),<br>Carbamazepine (Anticonvulsant),<br>Enzalutamide (Antiandrogen),<br>Ivosidenib (Cancer Treatment),<br>Lumacaftor (Cystic Fibrosis Treatment),<br>Mitotane (Antineoplastic),<br>Phenytoin (Anticonvulsant),<br>Rifampin (Antibiotic),<br>Rifapentine (Antibiotic),<br>St. John's wort extract (Herbal Medication) | 5 half-lives plus 14 days |
| **CYP3A Inducer (moderate)** | Asunaprevir and Beclabuvir and Daclatasvir (Antiviral),<br>Bosentan (Endothelin Receptor Antagonist),<br>Cenobamate (Anticonvulsant),<br>Dabrafenib (Kinase Inhibitor),<br>Efavirenz (Non-nucleoside Reverse Transcriptase Inhibitor),<br>Elagolix (Gonadotropin-releasing Hormone Receptor Antagonist),<br>Etravirine (Non-nucleoside Reverse Transcriptase Inhibitor),<br>Lersivirine (Non-nucleoside Reverse Transcriptase Inhibitor),<br>Lenisurad (Antigout and Uricosuric Agent),<br>Lopinavir (Protease Inhibitor),<br>Lorlatinib (Kinase Inhibitor),<br>Metamizole / Dipyrone (Analgesic),<br>Mitapivat (Pyruvate Kinase Activator),<br>Modafinil (Psychostimulant),<br>Nafcillin (Antibiotic),<br>Pexidartinib (Kinase Inhibitor),<br>Primidone (Anticonvulsant),<br>PF-06282999 (Myeloperoxidase Inactivator), | 5 half-lives plus 14 days |

[redacted]

| Drug Category | Drugs (Therapeutic Class) | Washout Period Requirement Prior to the First Dose of Study Intervention |
|---|---|---|
| | Phenobarbital (Anticonvulsant),<br>Rifabutin (Antibiotic),<br>Semagacestat (Alzheimer's Disease & Dementia Treatment),<br>Sotorasib (Kinase Inhibitor),<br>Talviraline (Non-nucleoside Reverse Transcriptase Inhibitor),<br>Telotristat Ethyl (Antidiarrheal),<br>Thioridazine (Antipsychotic),<br>Tipranavir and Ritonavir (Protease Inhibitor) | |
| **OATP (1B1/1B3) Inhibitor** | Atazanavir and Ritonavir (Protease Inhibitor),<br>Boceprevir (Antiviral),<br>Clarithromycin (Antibiotic),<br>Cyclosporine (Immunosuppressant),<br>Eltrombopag (Thrombopoietin receptor agonist)<br>Erythromycin (Antibiotic),<br>Faldaprevir (Antiviral),<br>Gemfibrozil (Fibric Acid Derivative),<br>Grazoprevir (Antiviral),<br>Itraconazole (Antifungal),<br>Letermovir (Antiviral),<br>Lopinavir and Ritonavir (Protease Inhibitor),<br>Rifampin, single dose (Antibiotic),<br>Simeprevir (Antiviral)<br>Telaprevir (Antiviral),<br>Velpatasvir (Antiviral) | 14 days or 5 half-lives, whichever is longer |
| **CYP2C19 Substrate[a]** | BMS-823778 (Diabetes Treatment),<br>Clobazam (Benzodiazepine),<br>Clopidogrel (Antiplatelet),[b]<br>Diazepam (Benzodiazepine),<br>Gliclazide (Sulfonylurea),<br>Hexobarbital (Hypnotic – Sedative),<br>Mephobarbital (Anticonvulsant),<br>Proguanil (Antimalarial),<br>S-mephenytoin (Anticonvulsant),<br>Tilidine (Treatment of Pain & Inflammation),<br>Valproic acid (Anticonvulsant) | 14 days or 5 half-lives, whichever is longer |
| **UGT1A1 Substrate** | Belinostat (Histone Deacetylase Inhibitor),<br>Irinotecan (Topoisomerase Inhibitor) | 14 days or 5 half-lives, whichever is longer |

a. The PPIs dexlansoprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole, although considered sensitive CYP2C19 substrates, are not listed above due to wide therapeutic index and no anticipated impact on their efficacy or safety.

[redacted]

| Drug Category | Drugs (Therapeutic Class) | Washout Period Requirement Prior to the First Dose of Study Intervention |
|---|---|---|

b. The PK interaction between PF-07081532 and clopidogrel has been clinically assessed (see PF-07081532 IB). Out of abundance of caution, until further clinical or model-based assessment of whether the modest changes in exposure observed can elicit any clinically meaningful impact on efficacy/safety, co-administration of PF-07081532 with clopidogrel is prohibited.

## 10.10. Appendix 10: Abbreviations

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

| Abbreviation | Term |
|---|---|
| abs | absolute |
| ADL | activity/activities of daily living |
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| AKI | acute kidney injury |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| $AUC_{24}$ | area under the concentration-time curve over 24 hours |
| $AUC_{inf}$ | area under the concentration-time curve to infinity |
| $AUC_{last}$ | area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration |
| $AUC_{tau}$ | area under the concentration-time curve at steady state over the dosing interval tau |
| AV | atrioventricular |
| AxMP | auxiliary medicinal product |
| BA | bioavailability |
| BBS | Biospecimen Banking System |
| BE | bioequivalence |
| β-hCG | β-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 |
| CL | clearance |
| $C_{last}$ | last quantifiable concentration |
| CL/F | apparent clearance |
| $C_{max}$ | maximum observed 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 |

| Abbreviation | Term |
|---|---|
| CT | clinical trial |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| CTMS | Clinical Trial Management System |
| %CV | percent coefficient of variation |
| CV | coefficient of variation |
| CYP | cytochrome P450 |
| DCT | data collection tool |
| DDI | drug-drug interaction |
| DICI | drug-induced cholestasis index |
| DIKI | drug-induced kidney injury |
| DILI | drug-induced liver injury |
| EC | ethics committee |
| ECC | emergency contact card |
| ECG | electrocardiogram or electrocardiography |
| eCrCl | estimated creatinine clearance |
| eCRF | electronic case report form |
| EDB | exposure during breastfeeding |
| E-DMC | External Data Monitoring Committee |
| EDP | exposure during pregnancy |
| EFD | embryo-fetal development |
| eGFR | estimated glomerular filtration rate |
| eSAE | electronic serious adverse event |
| ET | early termination |
| EU | European Union |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database) |
| FIH | first in human |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GI | gastrointestinal |
| GLP-1 | glucagon-like peptide-1 |
| GLP-1R | glucagon-like peptide-1 receptor |
| HbA1c | hemoglobin A1c |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HCVAb | hepatitis C antibody |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| HRT | hormone replacement therapy |
| IB | Investigator's Brochure |

| Abbreviation | Term |
|---|---|
| ICD | informed consent document |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ID | identification |
| IMP | investigational medicinal product |
| $lnAUC_{inf}$ | natural logarithm of $AUC_{inf}$ |
| $lnC_{max}$ | natural logarithm of $C_{max}$ |
| IND | Investigational New Drug |
| INR | international normalized ratio |
| $Log_e$ | natural logarithm |
| IP | Investigational Product |
| IPAL | Investigational Product Accountability Log |
| IRB | Institutional Review Board |
| IV | Intravenous(ly) |
| K | Proportionality constant for Bedside and Modified Schwartz Equations (kidney function) |
| $k_{el}$ | terminal phase rate constant |
| KDIGO | Kidney Disease Improving Global Outcomes |
| LBBB | left bundle branch block |
| LFT | liver function test |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MEN2 | multiple endocrine neoplasia type 2 |
| MoA | mechanism of action |
| MTC | medullary thyroid cancer |
| MQI | medically qualified individual |
| NA | not applicable |
| NIMP | noninvestigational medicinal product |
| NOAEL | no-observed-adverse-effect level |
| OATP | organic anion transporting polypeptide |
| PCRU | Pfizer Clinical Research Unit |
| PD | pharmacodynamic(s) |
| PE | physical examination |
| PI | principal investigator |
| PK | pharmacokinetic(s) |
| PO | oral |
| PPI | proton pump inhibitor |
| PSSA | Pfizer's Serious Adverse Event Submission Assistant |
| PT | prothrombin time |
| PVC | premature ventricular contraction/complex |
| QD | once daily |
| QTc | corrected QT interval |

[redacted]

| Abbreviation | Term |
|---|---|
| QTcF | QTc corrected using Fridericia's formula |
| QTL | quality tolerance limit |
| qual | qualitative |
| RBC | red blood cell |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| Scr | serum creatinine |
| Scys | serum cystatin C |
| SoA | schedule of activities |
| SOC | System Organ Class |
| SOP | standard operating procedure |
| SRSD | Single Reference Safety Document |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| $t_{½}$ | terminal half-life |
| T2DM | Type 2 diabetes mellitus |
| T bili | total bilirubin |
| TEAE | treatment-emergent adverse event |
| THC | tetrahydrocannabinol |
| $T_{max}$ | time for $C_{max}$ |
| UACR | urine albumin-creatinine ratio |
| UGT | uridine diphosphate glucuronosyltransferase |
| ULN | upper limit of normal |
| US | United States |
| $V_z/F$ | apparent volume of distribution |
| WBC | white blood cell |
| WOCBP | woman/women of childbearing potential |

## 11. REFERENCES

1. Orskov C, Holst JJ, Knuhtsen S, et al. Glucagon-like peptides GLP-1 and GLP-2, predicted products of the glucagon gene, are secreted separately from pig small intestine but not pancreas. Endocrinology. 1986;119(4):1467-75.

2. Kreymann B, Williams G, Ghatei MA, et al. Glucagon-like peptide-1 7-36: a physiological incretin in man. Lancet. 1987;2(8571):1300-4.

3. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol. 1997;273(5):E981-8.

4. Flint A, Raben A, Astrup A, et al. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest. 1998;101(3):515-20.

5. Bioavailability Studies Submitted in NDAs or INDS – General Consideration Guidance for Industry. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). April 2022, Clinical Pharmacology. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-studies-submitted-ndas-or-inds-general-considerations. Accessed: 12 Oct 2022.

6. Committee for Proprietary Medicinal Products (CPMP)/EMEA. Note for Guidance on the Investigation of Bioavailability and Bioequivalence, July 2001. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-investigation-bioavailability-bioequivalence_en.pdf. Accessed: 12 Oct 2022.

7. Rodrigues AD. Drug Interactions Involving 17α-Ethinylestradiol: Considerations Beyond Cytochrome P450 3A Induction and Inhibition. Clin Pharmacol Ther. 2022;111(6):1212-21.

8. Banholzer ML, Wandel C, Barrow P, et al. Clinical trial considerations on male contraception and collection of pregnancy information from female partner: update. Clin Transl Med 2016;5(1):23-37.

9. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737-49.