## Title Page

# A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, CROSSOVER, FIRST-IN-HUMAN STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE ASCENDING ORAL DOSES OF PF-06954522 IN HEALTHY ADULT PARTICIPANTS

| | |
|---|---|
| **Study Intervention Number:** | PF-06954522 |
| **Study Intervention Name:** | NA |
| **US IND Number:** | 167845 |
| **EudraCT/EU CT Number:** | NA |
| **ClinicalTrials.gov ID:** | NA |
| **Pediatric Investigational Plan Number:** | NA |
| **Protocol Number:** | C4001001 |
| **Phase:** | 1 |
| **Sponsor Legal Address:** | Pfizer Inc.<br>66 Hudson Boulevard East<br>New York, NY 10001 |

**Brief Title:** A Study to Learn How Different Amounts of the Study Medicine called PF-06954522 are Tolerated and act in the Body in Healthy Adults

## Document History

| Document | Version Date |
|---|---|
| Original protocol | 17 July 2023 |

## TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

### Protocol Title:

A Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, Crossover, First-in-Human Study to Assess the Safety, Tolerability, and Pharmacokinetics of Single Ascending Oral Doses of PF-06954522 in Healthy Adult Participants

### Brief Title:

A Study to Learn How Different Amounts of the Study Medicine Called PF-06954522 are Tolerated and Act in the Body in Healthy Adults

### Regulatory Agency Identification Number(s):

| | |
|---|---|
| **US IND Number:** | 167845 |
| **EudraCT/EU CT Number:** | NA |
| **ClinicalTrials.gov ID:** | NA |
| **Pediatric Investigational Plan Number:** | NA |
| **Protocol Number:** | C4001001 |
| **Phase:** | 1 |

### Rationale:

PF-06954522 is an orally administered small molecule glucagon-like peptide-1 receptor (GLP-1R) agonist that is being developed as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus (T2DM). The purpose of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of single ascending oral doses of PF-06954522 in healthy adult participants. This study is the first time that PF-06954522 is administered to humans. The safety, tolerability, and PK results obtained from this study will inform future clinical development of PF-06954522.

## Objectives and Endpoints:

| Objectives | Endpoints |
|---|---|
| **Primary:** | **Primary:** |
| • To evaluate the safety and tolerability of single oral doses of PF-06954522 administered to healthy adult participants. | • Assessment of AEs, safety laboratory tests, vital signs (blood pressure, pulse rate, respiratory rate and temperature), cardiac telemetry and standard 12-lead ECGs, and PE. |
| **Secondary:** | **Secondary:** |
| • To characterize the plasma PK of PF-06954522 following single oral doses of PF-06954522 administered to healthy adult participants. | • PF-06954522 PK parameters: $AUC_{last}$, $C_{max}$, $T_{max}$, and if data permit $AUC_{inf}$ and $t_{½}$. |

Abbreviations: AE = adverse event; $AUC_{inf}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinite time; $AUC_{last}$ = area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; $C_{max}$ = maximum plasma concentration; ECG = electrocardiogram; PE = physical examination; PK = pharmacokinetic(s); $t_{½}$. = terminal half-life; $T_{max}$ = time for $C_{max}$.

**Overall Design:** This study is a randomized, double-blinded (investigator- and participant-blinded), sponsor-open, first in human (FIH), single-ascending oral dose, 5-period crossover, placebo substitution design in 1 cohort of healthy adult participants. An optional cohort, enrolling healthy adult participants in up to 4 crossover periods, may be included to permit assessment of any of the following: repeat of a previously administered dose level; studying additional dose levels as dictated by the evaluated safety, tolerability, or PK of earlier dose levels; or any other assessment needed to meet the objectives of this study. A second optional cohort enrolling Japanese participants to receive PF-06954522 or placebo in up to 3 periods, may also be included.

**Number of Participants:** Approximately 24 healthy adult participants will be enrolled in the study. This includes up to approximately 10 healthy participants for Cohort 1, up to approximately 8 healthy participants for optional Cohort 2 and up to approximately 6 healthy Japanese participants for the optional Cohort 3. The actual number of Japanese participants may be adjusted based on emerging data or operational factors with a maximum sample size of up to 8 participants (6 receiving PF-06954522 and 2 receiving placebo in each period).

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 to study intervention.

**Study Population:**

Key inclusion and exclusion criteria are listed below:

**Inclusion Criteria**

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

1. Male and female participants of non-childbearing potential aged 18 to 65 years, inclusive, at screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

2. BMI of 16 to 30.5 kg/$m^2$; and a total body weight >50 kg (110 lb).

Note: participants enrolling as Japanese must have 4 biological Japanese grandparents who were born in Japan. A lower entry weight of 45 kg may be considered if the total blood volume collection for this cohort does NOT exceed 360 mL over an 8-week period.

**Exclusion Criteria**

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

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, gastrectomy, cholecystectomy).

    - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb, or HCVAb. History of hepatitis B vaccination with an isolated positive HBsAb result is allowed.

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

3. Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions 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, with the exception of CCI [redacted]

CCI which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention.

5. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Participation in studies of other investigational products (drug or vaccine) at any time during their participation in this study.

6. A positive urine drug test at Screening or admission.

7. Screening supine blood pressure (BP) ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of supine rest. If systolic BP is ≥140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, 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.

8. Renal impairment as defined by an estimated glomerular filtration rate (eGFR) of <75 mL/min/1.73 $m^2$. Based upon participant age at screening, eGFR is calculated using the recommended Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations to determine eligibility (Screat-based formula) and to provide a baseline (Screat-Scys combined formula) to quantify subsequent kidney safety events. For eligibility assessment based upon estimated renal function, the higher of the screening and baseline eGFR values may be used.

9. Standard 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 atrioventricular (AV) block, or serious bradyarrhythmias or tachyarrhythmias). If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice 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.

10. 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:

    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin ≥1.05 × upper limit of normal (ULN). Participants with an elevated total bilirubin consistent with Gilbert's Disease may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;

    - TSH > ULN;

    - HbA1c ≥6.5%;

- Hematuria as defined by ≥1+ heme on urine dipstick;
- Albuminuria as defined by urine albumin/creatinine ratio (UACR) >30 mg/g.

11. 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).

12. Use of tobacco or nicotine-containing products in excess of the equivalent of 5 cigarettes/day or 2 chews of tobacco/day.

13. 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.

**Study Arms and Duration:** The total duration of participation from the screening visit to the telephone follow-up contact will be approximately 15 weeks for each participant.

| **Study Intervention(s)** | | |
|---|---|---|
| **Intervention Name** | PF-06954522 | Placebo |
| **Use** | Experimental | Placebo |
| **IMP or NIMP/AxMP** | IMP | IMP |
| **Dose Formulation** | Bulk powder for extemporaneous preparation of oral suspensions | Bulk powder for extemporaneous preparation of oral suspensions |
| **Unit Dose Strength(s)** | CCI mg | 0 mg |
| **Route of Administration** | Oral | Oral |

| Study Arm(s) | | | |
|---|---|---|---|
| **Arm Title** | Cohort 1 | Cohort 2 (Optional) | Cohort 3 (Optional) |
| **Arm Description** | Participants may receive up to 5 dose levels of PF-06954522 and matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined. | Participants may receive up to 4 dose levels of PF-06954522 and matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined. | Participants may receive up to 3 dose levels of PF-06954522 and matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined. |

Assessment of the safety, tolerability, and PK after each single dose level will be conducted before escalating to the next dose level. The dose/exposure-escalation increments are planned to be up to approximate semi-logarithmic increases in exposure from the previous highest dose level that has been evaluated. The actual dose levels, target exposures, and/or dose level increments may be adjusted during the study based on emerging human safety, tolerability, and PK data, but projected exposures will not exceed the predefined human exposure limits.

**Statistical Methods:** The sample size has been chosen based on the need to minimize first exposure to humans of a new chemical entity and the requirement to conduct adequate safety, tolerability, and PK assessments at each dose level. All safety analyses will be performed on the safety analysis set, which is defined as all participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. The plasma PK parameters for PF-06954522 following oral dose administration will be derived from the plasma concentration-time profiles. Plasma PK parameters and concentrations of PF-06954522 will be descriptively summarized by dose (and fasting condition, and ethnicity, if appropriate) and nominal time, as appropriate.

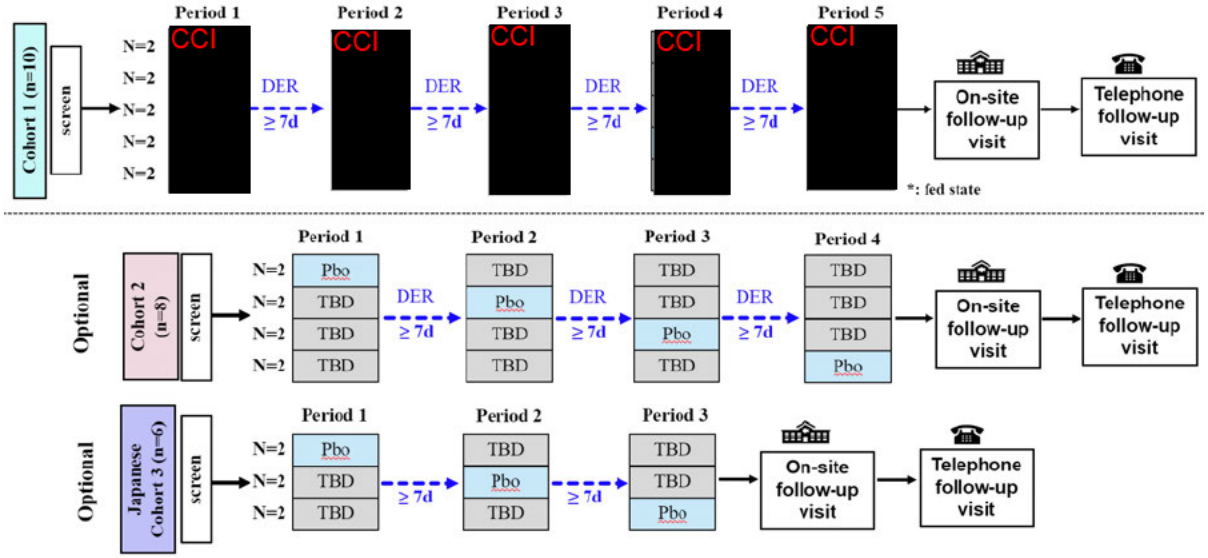
**Ethical Considerations:**

The participants in this study are not expected to obtain any specific benefit beyond contributing to the process of developing new therapies in an area of unmet need. They will be expected to commit time and may experience some discomfort while undergoing study procedures. However, they will receive close monitoring of their safety via safety monitoring procedures (eg, physical examinations, 12-lead ECGs, vital signs) as outlined in this protocol. Based on the totality of available nonclinical data and taking into account the measures to minimize risk to study participants, the overall benefit/risk profile supports clinical testing of PF-06954522 in this study as part of the clinical development of an adjunct to diet and exercise for the treatment type 2 diabetes mellitus (T2DM).

## 1.2. Schema

A sample study design schematic is presented in Figure 1. It should be noted that this is for illustrative purposes, only.

**Figure 1. Study Design Schematic: Sequential, Placebo-Controlled, 5-Period, Crossover Design**




- All doses in the schematic above (other than the starting dose of [redacted] mg) are **for illustrative purposes only**, as treatment sequences, actual doses and dose increments may be adjusted during the study based on emerging safety, tolerability and PK data.
- Each period will consist of admission on Day -1, dosing on Day 1, and discharge on Day 4. There will be a washout interval of at least 7 days between consecutive doses administered to an individual participant. The washout interval may be adjusted based on data emerging from previous cohorts/periods.
- Dose escalation to occur following review of PK data through at least 24 hours post-dose and safety and tolerability data through at least 48 hours post-dose of the current period. Cumulative safety and tolerability data from all previous periods will also be reviewed.
- It is anticipated that the effect of food (dose administration with a high fat breakfast) on PF-06954522 PK will be assessed in the last Period of Cohort 1. This will be assessed at a dose level (to be chosen based on emerging data) that has been previously administered fasted within the same cohort. However, the effect of food may be assessed during any of the study periods/cohorts if thought necessary to achieve study objectives.
- On-site follow-up visit to occur 7-10 days after administration of the final dose of study intervention. Follow-up contact may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.
- DER: dose escalation review; Pbo: placebo; TBD: to be determined.

### 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.

Please refer to Appendix 10 for abbreviations used in the SoA table and associated footnotes. Note that the symbol → denotes an activity that is continuous/ongoing for the indicated duration.

**Table 1. Study Schedule of Assessments**

| **Visit Identifier** Abbreviations used in this table may be found in Appendix 10. | **Screen** | **Period 1 to Period 5** | | | | | | **F/U Visit** | **F/U Contact** | **Early Discont** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **Day -28 to Day -2** | **Day -1** | **Day 1** | **Day 2** | | **Day 3** | **Day 4** | **Days 8-11** | **Days 29-36** | | There are 5 periods in Cohort 1, 4 and 3 periods for optional Cohorts 2 and 3, respectively. Follow-up contact 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** | **24** | **36** | **48** | **72** | | | | |
| Outpatient visit | X | | | | | | | X | | | F/U visit to occur 7-10 days after the final dose of study intervention (Period 4 only). |
| Informed consent | X | | | | | | | | | | Informed consent should be obtained prior to undergoing any study-specific procedures. See Section 10.1.3 for additional information |
| CRU confinement | | X | → | → | → | → | X | | | | Participants may be asked to remain at the CRU after completion of Day 4 activities at the discretion of the investigator or if safety, tolerability, or PK data (eg, $t_{½}$ is longer than expected) dictate the need to prolong confinement in the CRU. |
| Discharge from CRU | | | | | | | X | | | | |
| Demography | X | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | | Day -1 in Period 1 only. Review any changes from Screening. |
| Medical/medication history | X | X | | | | | | | | | Day -1 in Period 1 only. Review any changes from Screening. |

## Table 1. Study Schedule of Assessments

| **Visit Identifier** Abbreviations used in this table may be found in Appendix 10. | **Screen** | **Period 1 to Period 5** | | | | | | **F/U Visit** | **F/U Contact** | **Early Discont** | **Notes** |
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| **Days Relative to Day 1** | **Day -28 to Day -2** | **Day -1** | **Day 1** | **Day 2** | | **Day 3** | **Day 4** | **Days 8-11** | **Days 29-36** | | There are 5 periods in Cohort 1, 4 and 3 periods for optional Cohorts 2 and 3, respectively.<br>Follow-up contact 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** | **24** | **36** | **48** | **72** | | | | |
| History of alcohol, tobacco, and illegal drug use | X | X | | | | | | | | | Day -1 in Period 1 only. Review any changes from Screening. |
| Review concomitant treatments | X | X | → | → | → | → | → | X | X | X | See Section 6.9 for additional details. |
| Contraception check | X | X | | | | | X | X | X | X | Only required for male participants. Day -1 & Day 4 check not required between study periods if participant is not discharged from CRU. Contraceptive guidance is outlined in Appendix 4. |
| Physical exam | X | X | | | | | | | | X | Complete PE (including height and weight) at screening or upon admission in Period 1; brief PE performed any time for findings during previous exam or new/open AEs, at investigator discretion. See Section 8.3.1 for additional details. |
| Respiratory rate and oral body temperature | X | | See Table 2 | X | | | X | | | X | See Section 8.3.2.2 and Section 8.3.2.3 for additional details. |
| Supine BP and pulse rate | X | | | X | X | X | X | X | | X | Single supine blood pressure and pulse rate at screening, follow-up visit and ET. Triplicate measurements at all other times. See Section 8.3.2.1 for additional details. |
| 12-Lead ECG | X | | | X | X | X | X | X | | X | Single 12-lead ECG at screening, follow-up visit, and ET. Triplicate measurements at all other times. See Section 8.3.3 for additional details. |
| Continuous cardiac telemetry | | X | | | | | | | | | Baseline telemetry must be recorded for ≥2 hours while participant is awake in the 24 hours prior to dosing on Day 1 of Period 1. See Section 8.3.3.1 for additional details. |
| Serious and nonserious AE monitoring | X | → | → | → | → | → | → | → | X | X | See Section 8.4.3 for follow-up AE and SAE assessments. |

## Table 1. Study Schedule of Assessments

| **Visit Identifier** Abbreviations used in this table may be found in Appendix 10. | **Screen** | **Period 1 to Period 5** | | | | | **F/U Visit** | **F/U Contact** | **Early Discont** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **Day -28 to Day -2** | **Day -1** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Days 8-11** | **Days 29-36** | | There are 5 periods in Cohort 1, 4 and 3 periods for optional Cohorts 2 and 3, respectively.<br>Follow-up contact 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** | **24** | **36** | **48** | **72** | | | | |
| Blinded study intervention administration | | | See Table 2 | | | | | | | |
| Standardized meals/snack | | X | X | → | → | → | X | | | See Section 5.3.2. |
| **Blood sample for:** | | | | | | | | | | |
| Safety laboratory: hematology and chemistry | X | X | | X | | | X | X | | X | Participants must fast for ≥4 hours prior to any safety lab evaluation. See Section 5.3.2 for additional details. Day -1 results must be reviewed and confirmed acceptable prior to dosing. |
| Safety laboratory: calcitonin, amylase, lipase and total bile acids | X | X | | X | | | X | X | | X | Participants must fast for ≥4 hours prior to any safety lab evaluation. For total bile acids, an 8-hour fasting is required. See Section 5.3.2 for additional details. Review of these data is not required prior to dose escalation; cumulative results will be reviewed as they become available. |
| Serum FSH | X | | | | | | | | | | Only for postmenopausal women. |
| HbA1c, TSH, HBcAb, HBsAg, HBsAb, HCVAb and HIV | X | | | | | | | | | | See Appendix 2: Clinical Laboratory Tests. |
| Retained Research Sample for Genetics (Prep D1) | | | X | | | | | | | | Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.<br>Day 1 of Period 1 only |
| Retained Research Samples for Biomarkers [Prep B2.5] | | | See Table 2 | | | | | | | | To be collected as outlined in Section 8.7.2. |

## Table 1. Study Schedule of Assessments

| **Visit Identifier** Abbreviations used in this table may be found in Appendix 10. | **Screen** | **Period 1 to Period 5** | | | | | | **F/U Visit** | **F/U Contact** | **Early Discont** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Days Relative to Day 1** | **Day -28 to Day -2** | **Day -1** | **Day 1** | **Day 2** | | **Day 3** | **Day 4** | **Days 8-11** | **Days 29-36** | | There are 5 periods in Cohort 1, 4 and 3 periods for optional Cohorts 2 and 3, respectively.<br>Follow-up contact 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** | **24** | **36** | **48** | **72** | | | | |
| PF-06954522 PK blood sampling | | | | X | X | X | X | | | X | See Section 8.5 for additional details. |
| CCI | | | | | | | | | | | |
| **Urine sample for:** | | | | | | | | | | | |
| Urine drug testing | X | X | | | | | | | | | Results of any pre-dose testing to be confirmed acceptable prior to dosing. Day -1 testing not required between study periods if participant remains in CRU. |
| Urinalysis (with microscopy, if needed) | X | X | | X | | | X | X | | X | |
| Urine albumin/creatinine ratio | X | | | | | | | | | | |

**Table 2. Study Schedule of Assessments for PK, Vitals, and ECGs on Day 1 of Each Period**

| **Visit Identifier** Abbreviations used in this table may be found in Appendix 10. | **Period 1 to Period 5** | | | | | | | | | | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Day 1** | | | | | | | | | | | | |
| **Hours Relative to Dosing at 0 hour** | **-1.0** | **-0.5** | **0** | **0.5** | **1** | **2** | **3** | **4** | **6** | **8** | **10** | **12** | Day 1 activities at time = 0 hour are prior to the dose, except for study intervention administration. |
| Blinded study intervention administration | | | X | | | | | | | | | | Participants should fast for at least 10 hours prior to dosing, except for periods in which food effects are investigated. See Section 5.3.2 and Section 6.1.1 for additional information. |
| Standardized meals/snack | | | | | | | | X | | | X | | See Section 5.3.2. |
| Respiratory rate and oral body temperature | | | X | | | | X | | | X | | | See Section 8.3.2.2 and Section 8.3.2.3 for additional details. |
| Supine BP and pulse rate | | | X | X | X | X | X | X | X | X | X | | Triplicate measurements at all times. See Section 8.3.2.1 for additional details. In the optional cohort of Japanese participants, vital sign assessments may be performed at selected time-points to be decided based on emerging data from previous cohort(s). |
| 12-Lead ECG | X | X | X | X | X | X | X | X | X | X | X | | Triplicate measurements at all timepoints. See Section 8.3.3 for additional details.<br>In the optional cohort of Japanese participants, ECG assessment may be performed at selected time-points to be decided based on emerging data from previous cohort(s). |
| Continuous cardiac telemetry | | | X | → | → | → | → | → | → | X | | | Telemetry monitoring will not be performed in the optional cohort of Japanese participants. See Section 8.3.3.1 for additional details. |
| **Blood sampling for:** | | | | | | | | | | | | | |
| PF-06954522 plasma PK | | | X | X | X | X | X | X | X | X | X | X | See Section 8.5 for additional details. |
| CCI | | | | | | | | | | | | | |
| Retained Research Samples for Biomarkers [Prep B2.5] | | | X | | X | | | | | | | | To be collected as outlined in Section 8.7.2. |

## 2. INTRODUCTION

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

PF-06954522 is an orally administered small molecule GLP-1 receptor agonist that is currently being developed as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

### 2.1. Study Rationale

The purpose of this study is to evaluate the safety, tolerability and PK of single ascending oral doses of PF-06954522 in healthy adult participants. This study is the first time that PF-06954522 will be administered to humans. The safety, tolerability and PK results obtained from this study will inform future clinical development of PF-06954522.

### 2.2. Background

Diabetes is estimated to affect more than 500 million adults (aged 20-79) worldwide.[5] The increase in the global prevalence of T2DM is largely attributed to rising rates of excess body weight and obesity.[6] T2DM is characterized by insulin resistance, a disorder in which cells do not respond effectively to insulin, resulting in higher blood glucose levels. Elevated blood glucose levels and increasing severity of insulin resistance result in the need for more insulin over time, eventually resulting in progressive pancreatic β-cell failure.[7] Patients with poorly controlled T2DM have an increased risk of developing complications associated with both microvascular and macrovascular disease, including nephropathy, neuropathy, retinopathy, and cardiovascular disease; and are at 2 to 4 times increased risk of mortality when compared with adults who do not have diabetes.[8] While existing pharmacological options for the treatment of diabetes may provide satisfactory glycemic control for some patients, there remain a large number of patients who do not achieve target HbA1c levels, suggesting a need for additional therapeutic options which minimize patient burden such as oral therapies.

Currently available GLP-1R agonists have demonstrated robust efficacy for glycemic control, weight loss, and CV safety, with several agents having shown a benefit in CV outcomes.[9] Most available GLP-1R agonist treatment options are injected once weekly subcutaneously.[10],[11] Injectable therapies are often underutilized due to patient hesitancy, whereas oral options are preferred by many patients. Only one GLP-1R agonist (Rybelsus®; oral semaglutide) is currently commercially available for oral administration. However, oral semaglutide has strict administration requirements (food and water restrictions) and has limitations due to its low bioavailability[12], making it less convenient than an agent without such restrictions. A novel oral small molecule GLP-1R agonist that may further improve glycemic control, reduce HbA1c levels, and decrease food intake and body weight compared to existing oral GLP-1R agonist, without any administration restrictions, is expected to be a preferred therapeutic option for patients with T2DM and their physicians. Another small

molecule GLP-1R agonist (danuglipron) is also currently under development by Pfizer for the treatment of T2DM.

Brief summaries of nonclinical pharmacology, nonclinical PK and metabolism, biopharmaceutical properties and nonclinical safety are provided below. Additional details for these sections can be found in the IB.

### 2.2.1. Nonclinical Pharmacology

In vitro primary PD studies demonstrated that in cells expressing recombinant human and cynomolgus monkey GLP-1R, CCI [redacted] Administration of PF-06954522 led to a significant reduction in blood glucose and significant increase in plasma insulin level, relative to vehicle-treated humanized GLP-1R mice.

### 2.2.2. Nonclinical Pharmacokinetics and Metabolism

In rats and monkeys following single IV and oral dosing, PF-06954522 exhibited low $CL_p$ and low to moderate steady state $V_{ss}$, leading to a CCI [redacted]. Renal and biliary excretion of unchanged PF-06954522 was minimal in rats. After repeated oral doses of PF-06954522 to rats and monkeys, systemic exposure increased with increasing dose, with little to no accumulation observed.

PF-06954522 was similarly highly bound to rat, monkey, and human plasma proteins CCI [redacted] and preferentially distributed into plasma versus blood across the species. CCI [redacted].

Preliminary in vitro metabolism of PF-06954522 showed similar metabolic profiles in monkey and human with some differences in mouse, rat, rabbit, and dog and no evidence of human specific metabolites. CCI [redacted] Based on the regulatory FDA

and EMA DDI guidance documents, utilizing the measured CCI [redacted]

### 2.2.3. Biopharmaceutics

CCI [redacted]

### 2.2.4. Nonclinical Safety

PF-06954522 has been evaluated in nonclinical safety studies up to 8 weeks in rats and monkeys.

CCI [redacted] which were associated with nonadverse changes in hematology (increased reticulocytes) and nonadverse microscopic findings in the thymus (decreased lymphocyte cellularity), peri-aortic adipose tissue (decreased lipid content), and pancreas (decreased zymogen content). Nonadverse findings noted in animals surviving to scheduled necropsy included decreased food consumption, body weight and body condition score, decreased total triiodothyronine (without changes in thyroxine or thyroid stimulating hormone), and sporadic emesis.

In the GLP-compliant single-dose crossover safety pharmacology cardiovascular study in monkeys, CCI [redacted]

The only nonclinical species for which PF-06954522 activates the GLP-1 receptor is the monkey; therefore, toxicity studies in rats were used to evaluate off-target pharmacology. CCI [redacted] Adverse test article-related microscopic findings at CCI mg/kg/day contributing to the moribundity and death were noted in the heart of one animal (degeneration and necrosis of the myocardium complicated by the fact that this animal did not fully recover from anesthesia), nonglandular stomach (multifocal squamous epithelial hyperplasia in 1 animal), liver (multifocal areas of mixed cell inflammation with associated hepatocyte degeneration and necrosis), and lung (multifocal neutrophilic infiltrates throughout large and small airways). In animals that survived to scheduled necropsy nonadverse, test article-related effects compared with the control group included clinical observations, effects on food consumption and body weight, alterations in hematology CCI [redacted] and clinical chemistry parameters CCI [redacted], higher liver CCI [redacted], lower thymus weights and microscopic changes in the liver (hepatocellular hypertrophy) CCI [redacted] and in the nonglandular stomach (mild squamous cell epithelial hyperplasia o) CCI [redacted] mg/kg/day.

CCI [redacted] mg/kg/day compared with the control group. These findings were nonadverse due to limited severity and absence of liver necrosis, degeneration, or inflammation.

The NOAEL in the GLP 8-week toxicity studies in CCI [redacted].

PF-06954522 was not genotoxic in either in vitro or in vivo assays. There is no photo safety concern with PF-06954522.

### 2.3. Benefit/Risk Assessment

Study C4001001 is the first time that PF-06954522 will be administered to humans. For healthy participants participating in this single dose study, no clinical benefit is expected. The purpose of this study is to evaluate the safety, tolerability, and PK of single ascending oral doses of PF-06954522 in healthy adult participants; and provide the basis for further clinical development of PF-06954522 as a potential new, pharmacological agent for the

treatment of patients with T2DM. As of the date of this protocol, no specific human risks have been identified; postulated risks based on nonclinical studies with PF-06954522 and marketed GLP-1R agonists are summarized in Section 2.3.1. The clinical impact of any potential risks will be minimized through the proposed cautious dose escalation process wherein higher doses of PF-06954522 will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile (Section 4.2 and Section 4.3). In addition, this study will employ stopping rules for dose escalation (Section 6.6.1) and includes standard, intensive, inpatient monitoring of the participants following administration of single, oral doses of the study intervention as outlined in the SoA.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06954522 may be found in the IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

### 2.3.1. Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention(s) PF-06954522** | | |
| Gastrointestinal adverse reactions | The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide, semaglutide and dulaglutide). | Study includes inpatient monitoring of the participants following administration of a single dose of the study intervention. Participants are monitored to prevent potential sequelae of any severe gastrointestinal reactions, eg, dehydration. |
| 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 participants enrolled will not have diabetes and will not be receiving anti-diabetic agents.<br>Study includes inpatient monitoring of the participants following administration of a single dose of the study intervention. |
| Increased heart rate and decreased PR interval | 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. Increased heart rate and decreased PR interval was observed in a single-dose NHP study of PF-06954522. | Study includes inpatient monitoring of the participants through periodic vital sign assessment, ECGs and telemetry following administration of a single dose of the study intervention. |
| 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, suicidal ideation/behavior and acute gallbladder disease. | These potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, dulaglutide, exenatide and semaglutide). | This is a single dose study in healthy participants.<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.<br>Study includes inpatient monitoring and safety laboratory surveillance (eg, calcitonin, amylase, lipase, eGFR) of the |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention(s) PF-06954522** | | |
| | | participants following administration of a dose of the study intervention. |
| Increased transaminases (eg, ALT & AST) | Elevated ALT and AST were observed in a subset of participants in the lotiglipron clinical studies following multiple dose administration. | Study includes inpatient monitoring and safety laboratory surveillance (eg, LFTs) of the participants following administration of a dose of the study intervention. |

### 2.3.2. Benefit Assessment

The participants in this study are not expected to obtain any specific benefit beyond contributing to the process of developing new therapies in an area of unmet need.

### 2.3.3. Overall Benefit/Risk Conclusion

Based on all available data on PF-06954522, as well as data available for other GLP-1-R agonists and considering the measures to minimize risk to study participants, the potential risks identified in association with PF-06954522 are justified by the anticipated benefits that may be afforded to participants with T2DM.

## 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary:** | **Primary:** |
| • To evaluate the safety and tolerability of single oral doses of PF-06954522, administered to healthy adult participants. | • Assessment of AEs, safety laboratory tests, vital signs (blood pressure, pulse rate, temperature), cardiac telemetry and standard 12-lead ECGs, and PE. |
| **Secondary:** | **Secondary:** |
| • To characterize plasma PK of PF-06954522 following single oral doses of PF-06954522 administered to healthy adult participants. | • PF-06954522 PK parameters: $AUC_{last}$, $C_{max}$, $T_{max}$, and if data permit, $AUC_{inf}$ and $t_{½}$. |
| **Tertiary/Exploratory:** | **Tertiary/Exploratory:** |
| • To further characterize plasma PK of PF-06954522 following single oral doses of PF-06954522 administered to healthy adult participants.<br>• Optional: to characterize the effect of food (high-fat breakfast) on the plasma PK of PF-06954522 following single oral doses of PF-06954522 in healthy adult participants. | • Additional PF-06954522 PK parameters: $AUC_{last}$(dn), $C_{max}$(dn), and if data permit, $AUC_{inf}$(dn), CL/F, and $V_z$/F.<br>• PF-06954522 PK parameters after a high-fat meal: $AUC_{last}$, $C_{max}$, $T_{max}$ and if data permit, $AUC_{inf}$, CL/F, $V_z$/F and $t_{½}$. |
| CCI | |
| • Optional: to explore the safety, tolerability, and plasma PK of PF-06954522 in healthy adult Japanese participants. | • Assessment of AEs, safety laboratory tests, vital signs (blood pressure, pulse rate and temperature), standard 12-lead ECGs and the following PF-06954522 PK parameters in Japanese participants: $AUC_{last}$, $C_{max}$, $T_{max}$, and if data permit, $AUC_{inf}$, CL/F, $V_z$/F and $t_{½}$. |

## 4. STUDY DESIGN

### 4.1. Overall Design

This FIH study has a double-blinded (investigator- and participant blinded), sponsor-open, randomized, single-ascending oral dose, up to 5 period crossover, placebo substitution design in 1 cohort (Cohort 1) of healthy adult participants. An optional cohort of healthy adult participants (Cohort 2) in up to 4 crossover periods, may be included to permit assessment of any of the following: repeat of a previously administered dose level; studying additional dose levels as dictated by the evaluated safety, tolerability, or PK of earlier dose levels; or any other assessment needed to meet the objectives of this study. A second optional cohort (Cohort 3) enrolling Japanese participants in up to 3 crossover periods, may be included.

A total of approximately 24 healthy adult participants will be randomized, up to approximately 10 in Cohort 1, up to approximately 8 in optional Cohort 2, and up to approximately 6 Japanese participants in optional Cohort 3. The actual number of Japanese participants may be adjusted based on emerging data or operational factors, with a maximum sample size of up to 8 participants. Each participant, depending on the cohort to which they are enrolled, will be randomized to receive up to 5 and 4 single doses of PF-06954522 for Cohorts 1 and 2, respectively, and up to 2 placebo doses. In each period, approximately 8 and 6 participants in Cohorts 1 and 2, respectively, will receive a single dose of PF-06954522, and approximately 2 participants will receive placebo. In the optional cohort of Japanese participants, each participant will be randomized to receive up to 2 single doses of PF-06954522 and 1 placebo dose. The actual dose levels and design of this optional cohort of Japanese participants will be decided based on emerging data. This cohort, if implemented, will not be part of dose escalation as the dose levels administered would have been investigated and deemed sufficiently safe in previous cohort(s). Full details will be provided to the investigator in writing, prior to dosing of this cohort. Participants who discontinue for non-safety reasons prior to completion of the study may be replaced, at the discretion of the PI and sponsor. The replacement participant(s) may or may not be required to complete all periods of the cohort in which they are participating at the discretion of the PI and sponsor.

Participants will be screened within 28 days of their first dose of study intervention (Period 1, Day 1). Participants will be admitted to the CRU on Day -1 of each study period and will remain in the CRU through at least the 72-hour assessments on Day 4. Participants may remain in the CRU after completion of Day 4 activities at the discretion of the investigator or if safety, tolerability, or PK data dictate the need to prolong confinement in the CRU. Participants will receive a single oral dose of PF-06954522 or placebo on Day 1 of each period.

Between each dose administration to a given participant there will be a washout interval of at least 7 days. The washout interval may be increased based on data emerging from previous cohorts/periods. Dose escalation will occur only after the previous dose level was demonstrated to be well tolerated with an acceptable safety profile based on review of the emerging safety and PK data (see Section 6.6.1). Dose levels will be escalated to bracket the expected clinical dose range, but the projected exposures will not exceed the predefined human exposure limits. An on-site follow-up visit and a telephone follow-up contact will take place 7-10 days and 28-35 days, respectively, after the last dose of study intervention in the final period, or after early discontinuation. At the discretion of the investigator, telephone follow-up contact may be substituted with an on-site visit in case of additional follow-up of open AEs or clinically significant laboratory findings. Therefore, the total planned duration of participation, from the Screening visit to the follow-up phone call, will be approximately 13 weeks for Cohort 1, 12 weeks for optional Cohort 2 and 11 weeks for optional Cohort 3 (if performed as a 3-way crossover).

Dosing of study intervention is anticipated to occur following a fast of at least 10 hours. Dose administration may also occur in the fed state (following a high-fat breakfast, see Section 5.3.2), in order to explore any potential food effect on PF-06954522 PK. If this assessment is conducted, it is anticipated that the study intervention will be administered in

the fed state in the last period of Cohort 1 at a dose level that has been previously administered fasted within the same cohort. The actual dose level may be adjusted based on emerging data. Design of randomization will be flexible to allow for participants who received active treatment or placebo in fasted state at the dose level of interest to also receive the same treatment in the food effect period (thus allowing within-participant comparisons of fed versus fasted for approximately 8 participants on active treatment, see Figure 1). If thought necessary to achieve study objectives (eg, to assess tolerability or exposure), study treatment may be administered in the fed state (high-fat or standard breakfast) during any of the study periods/cohorts.

A sample design overview is shown in Section 1.2. Treatment sequences, actual doses and dose increments may be adjusted during the study based on emerging safety, tolerability and PK data.

### 4.2. Scientific Rationale for Study Design

As is typical in the case for FIH studies, the population planned for this study will be healthy adult male and female participants of nonchildbearing potential. Female participants will be confirmed not to be of childbearing potential because reproductive toxicity studies with PF-06954522 have not been conducted. In male participants, appropriate measures are expected to be followed to minimize potential transfer of PF-06954522 via semen to partners (see Appendix 4).

The highest anticipated $C_{max}$ and $AUC_{24}$ of PF-06954522 will not exceed the pre-defined human exposure stopping limits. Furthermore, to permit an unbiased assessment of safety, the participants' treatment assignments (active treatment versus placebo) will be blinded to both site staff (except those involved in preparation of doses) as well as the study participants. However, to permit real-time review of the safety, tolerability, and PK data, a limited number of sponsor study team members will be unblinded.

Given the current study is the first time PF-06954522 will be administered to humans, an escalating single, oral dose crossover design is planned with careful assessment and ongoing review of safety, tolerability, and PK data of PF-06954522. The crossover design will permit both a within- and between-participant assessment of safety/tolerability and PK at multiple dose levels and placebo. The optional Cohort 2 may be included if, based on emerging data from the Cohort 1, it is deemed necessary to meet the objectives of this study.

The optional Cohort 3 (Japanese participants) is included in this study to potentially collect safety, tolerability and PK data that may facilitate development of PF-06954522 in Japan. Continuous cardiac monitoring via telemetry will not be performed in this cohort, and the schedule of ECG/vital sign measurements may be less intensive (see SoA), because the doses administered in this cohort would have been investigated and deemed sufficiently safe in a previous cohort.

For a given participant, it is planned that dosing will be separated by at least 7 days. This planned washout interval is deemed sufficient CCI [redacted] (see Section 4.3.1). In addition, PK samples are planned to be collected over 72 hours post-dose to ensure sufficient characterization of PK profile and to account for any

uncertainty in PK prediction. However, sampling times, duration of sampling, and/or the length of the interval between doses may be modified and/or extended based on emerging PK. The planned doses in the dose escalation sequence (Table 3) may be modified or repeated, as guided by emerging safety, tolerability, and PK data but will follow the dose-escalation rules defined in Section 6.6.1.

Dosing will initially be conducted in the fasted state (at least 10 hours) to facilitate management of any AEs which may occur shortly after dosing. CCI [redacted] However, as it is expected that in future studies PF-06954522 may be administered in the fed state, the effect of food (high-fat breakfast) will be assessed in this study to explore not only the PK but also the safety and tolerability profile of PF-06954522 in the condition which it will be most likely administered in the next stages of development.

CCI [redacted]

Changes in temperature and blood pressure were also noted in nonclinical toxicity studies, and these parameters will be measured through serial assessments of vital signs. In addition, calcitonin, amylase, lipase, and total bile acids will be assessed in the study due to elevations (total bile acids) observed in nonclinical toxicity studies (see Section 2.2.4), and these laboratory parameters have been shown to increase in patients treated with marketed GLP-1R agonists.[13] Similarly, based on the potential risk of thyroid C-cell tumor associated with marketed GLP-1R agonists, participants with a personal or family history of MTC or MEN2, or participants with suspected MTC will be excluded. To ensure that participants with undiagnosed diabetes or thyroid dysfunction are not enrolled, HbA1c, and TSH levels will also be assessed at screening.

### 4.2.1. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of PF-06954522 have not been conducted. Therefore, female participants will be confirmed to be of non-childbearing potential, the use of a highly effective method of contraception is required for male study participants (see Appendix 4), and is recommended for partners of male participants who are WOCBP.

## 4.3. Justification for Dose

### 4.3.1. Human PK Prediction

Human PK of PF-06954522 were predicted using a combination of human in vitro and nonclinical in vivo data. CCI [redacted]

### 4.3.2. Predicted Human Efficacious Dose and Concentration

CCI [redacted] This dose of PF-06954522 has been predicted based on exposure-response modeling of CCI [redacted] and is projected to achieve a similar pharmacological response CCI [redacted]

CCI [redacted]

### 4.3.3. Human Exposure Stopping Limits

The NOAEL doses in the 8-week GLP toxicity studies were CCI [redacted], which were the highest doses tested in those respective studies. At the NOAEL in monkeys (the most sensitive toxicology species), the total $C_{max}$ and $AUC_{24}$ were CCI [redacted] ng/mL and CCI [redacted] ng•h/mL, respectively. Therefore, the human exposure stopping limits for PF-06954522 are based on the unbound exposures (CCI [redacted]) observed at the NOAEL in monkeys in the 8-week GLP toxicity study. After correcting for species dependent plasma protein binding in monkeys and humans:

- The human PF-06954522 total $C_{max}$ limit is CCI [redacted] ng/mL.
- The human PF-06954522 total $AUC_{24}$ limit is CCI [redacted] ng•h/mL.

### 4.3.4. Rationale for Dose Selection

The safety, tolerability, and plasma PK of PF-06954522 after administration of single escalating oral doses across a wide dose/exposure range will be evaluated in this study. The starting dose and subsequent dose escalation steps proposed in this study were determined using the projected human PK of PF-06954522, the available nonclinical safety data, and the anticipated pharmacological effect, and considering that this is a well-precedented mechanism for which multiple GLP-1R agonists are marketed products.

CCI [redacted]

Considering all the above along with the precedent of the pharmacological mechanism (in addition to the marketed peptide GLP-1R agonists, several oral small molecule GLP-1R agonists are in clinical development)[14,15], it is anticipated that the C[redacted] mg starting dose is

low enough to ensure high confidence in participant safety, while some pharmacological effects are expected.

The dose range to be studied was selected to account for uncertainties in the projected $C_{eff}$ and the projected therapeutic dose, while also bracketing the expected clinically efficacious dose range in humans for clinically relevant pharmacological activity and providing safety coverage for a wide range of PF-06954522 doses.

The projected exposures of PF-06954522 for each planned dose level, as well as the corresponding safety margins relative to human exposure limits are summarized in Table 3.

**Table 3. Predicted Human Exposure and Safety Margins Following Administration of Single Oral Doses of PF-06954522**

| Dose (mg)[a] | Predicted Human PF-06954522 Exposure | | | | Predicted Safety Margin | |
|---|---|---|---|---|---|---|
| | Total $C_{max}$[b] (ng/mL) | Total $AUC_{24}$[b] (ng•h/mL) | Unbound $C_{max}$[c] (ng/mL) | Unbound $AUC_{24}$[c] (ng•h/mL) | $C_{max}$[d] | $AUC_{24}$[d] |
| CCI | | | | | | |

a. Based on the available safety, tolerability and PK data, dose escalation may be adjusted to doses other than those outlined above with intermediate doses evaluated instead of or in addition to the planned dose levels with increments being approximately ≤½-log (ie, approximately 3.3-fold) while always following dose escalation and stopping rules outlined in Section 6.6.1.

b. Human PK profiles were predicted using a 1-compartment PK model with first-order absorption and elimination. The projected human PF-06954522 PK parameters outlined in Section 4.3.1 were used in the model.

c. Unbound exposure values calculated after correcting for plasma protein binding in humans (CCI ).

d. Safety margins at the proposed doses were calculated based on the human exposure limits (total CCI ) which were based on the NOAEL exposures in the 8-week NHP GLP toxicity study after correcting for species difference in plasma protein binding.

Beyond the starting dose, the planned dose escalation procedure will be dictated by the rules summarized in Section 6.6.1. Assessment of the safety, tolerability, and PK after each single dose level will be conducted before escalating to the next dose level. The dose/exposure-escalation increments are planned to be up to approximate semi-logarithmic increases in exposure from the previous highest dose level that has been evaluated. If exposure exceeds the projected therapeutic range, or if changes in safety parameters are observed, smaller dose-escalation steps may be implemented. Dose-escalation is envisioned to proceed up to the highest dose deemed to be well tolerated with an acceptable safety profile, achievement of plasma exposures equivalent to the PK stopping limits (see Section 6.6.1).

The actual dose levels, target exposures, and/or dose level increments may be adjusted (higher or lower) during the study based on emerging human safety, tolerability, and PK data, but projected exposures will not exceed the predefined human exposure limits. Dose levels may also be repeated if warranted.

When the assessment of the effect of food on the PK of PF-06954522 is conducted, the dose level will be selected based on emerging safety, tolerability, and PK data from previous periods of this study. This will be assessed at a dose level that has been previously administered fasted within the same cohort (as outlined in Section 4.2).

### 4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

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

## 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. If 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, 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 of non-childbearing potential aged 18 to 65 years, inclusive, at screening who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

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

**Other Inclusion Criteria:**

2. BMI of 16-30.5 kg/m$^2$; and a total body weight >50 kg (110 lb).

   **Japanese participants only:** participants enrolling as Japanese must have 4 biological Japanese grandparents who were born in Japan. A lower entry weight of

45 kg may be considered if the total blood volume collection for this cohort does NOT exceed 360 mL over an 8-week period.

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

4. 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, gastrectomy, cholecystectomy).

   - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb, or HCVAb. History of hepatitis B vaccination with an isolated positive HBsAb result is allowed.

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

3. Any medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions 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 with the exception of CCI [redacted] which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

**Prior/Concurrent Clinical Study Experience:**

5. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer). Participation in studies of other investigational products (drug or vaccine) at any time during their participation in this study.

**Diagnostic Assessments:**

6. A positive urine drug test at screening or admission.

7. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of supine rest. If systolic BP is ≥140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, 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.

8. Renal impairment as defined by an eGFR of <75 mL/min/1.73 m². Based upon participant age at screening, eGFR is calculated using the recommended CKD-EPI equations in Section 10.7.2 to determine eligibility (Screat-based formula) and to provide a baseline (Screat-Scys combined formula) to quantify subsequent kidney safety events. For eligibility assessment based upon estimated renal function, the higher of the screening and baseline eGFR values may be used.

9. Standard 12-lead ECG at Screening 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 QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice 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.

10. 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:

    - ALT, AST, or bilirubin ≥1.05 × ULN. Participants with an elevated total bilirubin consistent with Gilbert's Disease may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;
    - TSH > ULN
    - HbA1c ≥6.5%;

- Hematuria as defined by ≥1+ heme on urine dipstick;
- Albuminuria as defined by urine albumin/creatinine ratio (UACR) >30 mg/g.

**Other Exclusion Criteria:**

11. 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).

12. Use of tobacco/nicotine containing products in excess of the equivalent of 5 cigarettes/day or 2 chews of tobacco/day.

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

### 5.3. Lifestyle Considerations

The following guidelines are provided:

#### 5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

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) for at least 8 hours prior to all safety laboratory evaluations.

- Participants must abstain from all food and drink (except water) for at least 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.

**Dosing under fasted conditions (Day 1 only):**

- The standard morning breakfast will not be offered on Day 1. Participants will remain fasted for 4 hours following dosing.

**Dosing under fed conditions (Day 1 only):**

- A morning meal will be served to participants approximately 30 minutes prior to dosing and is expected to be completed approximately 10 minutes prior to dosing. Participants will be encouraged to consume the entire meal.

    - For planned assessment of food effect, this morning meal will be a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800-1000 calories) breakfast. The breakfast will consist of approximately 150 protein calories, 250 carbohydrate calories, and 500-600 fat calories. An example test meal would be: 2 eggs fried in butter, 2 strips of bacon (or 50 g of meat or sausage), 2 slices of toast with butter, 4 ounces (approximately 112 grams) of hash brown potatoes, and 8 fluid ounces (240 mL) of whole milk.

    - A standard breakfast may be provided during other study periods/cohorts, if deemed necessary to meet study objectives (see Section 4.1). If this is the case, details will be provided to the investigator in writing.

- While inpatient, the meals consumed are expected to follow the restrictions outlined below:

    - No food will be allowed for at least 4 hours post-dose.

    - Lunch will be provided approximately 4 hours after dosing.

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

- Participants may delay or skip postdose meals or be offered an alternative meal in case of nausea or vomiting. In such cases, the proportion of each meal consumed by the participants will be recorded.

- An evening snack may be permitted.

- On non-dosing days while inpatient, as appropriate, standard morning meal, lunch, and evening meal (along with an evening snack) are to be provided at a similar clock time to the clock time when these meals are offered on the dosing day.

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

- With the exception of the standard high-fat, high-calorie breakfast to be consumed during food effect assessment, while participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein, except when the study intervention is administered with high-fat, high-calorie breakfast. 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 may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

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

### 5.3.4. Activity

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

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

- Participants will be confined to the procedure room for the first 4 hours after dosing on Day 1 during continuous cardiac monitoring, except to use the bathroom. After this, if the equipment setup allows, participants may be ambulatory during the ECG monitoring period, but should not engage in strenuous activities. If equipment does not allow ambulation, appropriate accommodations will be made by the investigator site to facilitate continuous monitoring (eg, bedside urinals should be provided to accommodate participants' excretory needs).

### 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 discretion of the PI in consultation with the medical monitor.

## 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and, 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-06954522 and placebo.

### 6.1. Study Intervention(s) Administered

| Study Intervention(s) | | |
|---|---|---|
| **Intervention Name** | PF-06954522 | Placebo |
| **Type** | Drug | Drug |
| **Use** | Experimental | Placebo |
| **IMP or NIMP/AxMP** | IMP | IMP |
| **Dose Formulation** | Bulk powder for extemporaneous preparation of oral suspensions | Bulk powder for extemporaneous preparation of oral suspensions |
| **Unit Dose Strength(s)** | Planned suspension doses ranging from C[redacted] mg C | 0 mg |
| **Dosage Level(s)** | Single ascending doses CCI [redacted] mg (see Section 1.2 and Section 4.3.4) | 0 mg |
| **Route of Administration** | Oral | Oral |

| Study Intervention(s) | | |
|---|---|---|
| **Sourcing** | Provided by the sponsor | Provided by the sponsor |
| **Packaging and Labeling** | Study intervention will be provided in bulk powder for extemporaneous preparation of oral suspensions. Each bottle will be labeled as required per country requirement. | Study intervention will be provided in bulk powder for extemporaneous preparation of oral suspensions. Each bottle will be labeled as required per country requirement. |
| **SRSD** | IB | IB |

| Study Arm(s) | | | |
|---|---|---|---|
| **Arm Title** | Cohort 1 | Cohort 2 (Optional) | Cohort 3 (Optional) |
| **Arm Description** | Participants may receive up to 5 dose levels of PF-06954522 and matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined. | Participants may receive up to 4 dose levels of PF-06954522 and matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined. | Participants may receive up to 3 dose levels of PF-06954522 and matching placebo. Doses will be administered as oral suspensions as escalating single doses to be determined. |

PF-06954522 and placebo will be provided by Pfizer as bulk powders for extemporaneous preparation of oral suspensions at the CRU.

- PF-06954522 or placebo oral suspensions will be extemporaneously prepared for single oral doses ranging from CCI [redacted] mg.

PF-06954522 and placebo will be presented to the participants in individual dosing containers.

### 6.1.1. Administration

For fasted periods:

- Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours) without breakfast on Day 1.

For fed period(s):

- Following an overnight fast of at least 10 hours, participants will receive breakfast approximately 30 minutes prior to dosing on Day 1 which is to be completed within approximately 20 minutes as outlined in Section 5.3.2. The participants will then receive study intervention approximately 10 minutes after completion of the meal at approximately 0800 hours (plus or minus 2 hours).

On Day 1 of each period, investigator site personnel will administer a single oral dose of study intervention with ambient temperature water to a total volume of approximately 240 mL. Study intervention will be administered according to the EDR.

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

Administration of study intervention(s) at the site will be performed by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

Following administration of study intervention(s) at the site, participants will be observed for up to 2 hours post-dose by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

### 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 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.

PF-06954522 and placebo oral dosing suspensions will be prepared in the CRU by 2 operators, 1 of whom is a pharmacist. Details of dose preparation will be given in a separate EDR. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

PF-06954522 and placebo will be prepared by qualified unblinded site personnel according to the EDR. Blinded study intervention will be administered in a blinded fashion to the participant.

## 6.3. Assignment to Study Intervention

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 a double-blind (sponsor-unblinded) study.

### 6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

### 6.4.2. Blinding of Site Personnel

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

Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

In order to maintain this blind, an otherwise uninvolved third party will be responsible for the preparation and dispensing of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense or visual presentation, following randomization or dispensing. This third party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study intervention with the investigator.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

PCRU pharmacy staff responsible for preparing all study interventions will be unblinded. PCRU site staff providing technical system support to pharmacy staff and supporting blinded laboratory data processes will be unblinded. These site staff providing system support will not be involved in any data collection or clinic floor activities.

### 6.4.3. Blinding of the Sponsor

As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK modeling, and/or supporting clinical development. Individual participant-level unblinded data will be reviewed by a designated limited number of sponsor personnel.

### 6.4.4. Sensitive Clinical Data

Sensitive clinical data are data collected in this study that have the potential to unblind a participant's treatment assignment. Access to sensitive clinical data will be restricted to authorized individuals until the study has been unblinded. The following data variables are considered sensitive clinical data:

- Study intervention assignments (PF-06954522 or placebo);
- Individual PF-06954522 PK data.

### 6.4.5. Breaking the Blind

The method for breaking the blind in this study will be manual. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to

unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data; and provide information necessary to potentially alter the dose escalation- sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

### 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. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

### 6.6. Dose Modification

The decision to proceed to the next dose level of PF-06954522 (either an increase, decrease, or repeat of a previous dose level) will be made by the study team and the investigator based on observed safety, tolerability, and preliminary PK data obtained at the prior dose level. At least 8 and 6 participants (including at least 1 placebo participant) must complete the prior dose level in Cohort 1 and 2, respectively. PK data through at least 24 hours post-dose and safety and tolerability data through at least 48 hours post-dose of the current period will be reviewed. Cumulative safety and tolerability from all previous periods will also be reviewed.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, tolerability, and/or PK findings at a given dose level or to add cohorts to evaluate additional dose levels or repeat dose levels. The study procedures for these additional participant(s)/cohort(s) will be the same as that described for other study participants/cohorts unless otherwise indicated.

### 6.6.1. Dose Escalation and Stopping Rules

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not overrule the investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the study intervention.

The dose escalation will be terminated based on the following criteria:

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities, in the same organ class, indicating dose-limiting intolerance.

- Severe nonserious AEs, considered as, at least, possibly related to study intervention administration, in 2 participants at a given dose level (but not participants receiving placebo), independent of within or not within the same system organ class, indicating dose-limiting intolerance.

- Dosing will be paused for any SAE that occurs in a participant receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug-related by the PI and sponsor. If the SAE is determined to be either drug-related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.

- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.

- Other findings that, at the discretion of the study team and investigator, indicate that dose escalation should be halted.

- If, at any dose level, the average exposure reaches or exceeds the PK stopping limits: CCI [redacted].

- If, based on the observed data, the group mean $C_{max}$ or AUC (based on total plasma concentration) of the next planned dose is projected to exceed the escalation limits, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

- The highest dose evaluated in this study will not exceed [redacted] mg.

Progression to the next dose will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data.

### 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.

### 6.8. Treatment of Overdose

For this study, any dose of PF-06954522 projected to result in exposures greater than the defined PK stopping limit of [redacted], (see Section 6.6.1) 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 follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
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 2 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).

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

### 6.9. Prior and Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention with the exception of [redacted] which are prohibited within 14 days plus 5 half-lives prior to the first dose of study intervention (see Appendix 9).

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

Females taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study.

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.

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

### 7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following: AEs or other (administrative) reasons.

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for ongoing AEs. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

#### 7.1.1. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR or eCrCl) require expedited evaluation to differentiate AKI from DICI. DICI is defined as transporter-mediated effect related to altered renal tubular creatinine handling without histological injury.

**AKI** may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI and from DICI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.

**Follow-up Assessments**

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results.

Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals.

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR, eCrCl and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Appendix 7.

Assessments of urine albumin-to-creatinine ratio or urine volume may also be performed as appropriate.

If appropriate, nephrology consultation may be recommended to facilitate differentiation of renal parenchymal disease, pre-renal azotemia, and post-renal obstruction.

**Differentiating Acute Kidney Injury from DICI**

A confirmed Screat increase is defined as:

(i) ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR
(ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Based on the assessments performed, suspected AKI (including DIKI) may be differentiated from DICI as follows.

**Adult participants**

| | **AKI (including DIKI)**<br>**Any one of the below** | **DICI** |
|---|---|---|
| Scys & Screat | Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase | Confirmed Screat increase without confirmed increase in reflex Scys<br>AND<br>Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease. |
| eGFR | Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available) | |
| Albuminuria or proteinuria | Confirmed albuminuria increase (see Appendix 7 for Grades A1 to A3 quantitation) | |
| Urine volume | Urine volume <0.5 mL/kg/h for 6 consecutive hours | |

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either there is (i) new-onset or worsening albuminuria or proteinuria are detected.

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

### 7.1.2. Liver Injury

A participant who meets any of the following will be withdrawn from the study intervention.[16]

- ALT or AST >8 × ULN;
- ALT or AST >5 × ULN for more than 2 weeks;
- ALT or AST >3 × ULN **and** (T bili >2 × ULN **or** INR >1.5);
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

See Section 10.6 for Potential Cases of Drug Induced Liver Injury.

### 7.1.3. ECG Changes

A participant who meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from the study intervention.

- QTcF >500 ms.
- Change from baseline: QTcF >60 ms and QTcF >450 ms.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

### 7.1.4. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

## 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:

- Refused further study procedure;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the participant to comply with the protocol required schedule of study visits or procedures.

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 return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. 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 and Baseline Procedures

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

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

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

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

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

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

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

Any safety, laboratory or analyte results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

If done around the time of a blood draw, ECGs and vital sign assessments (BP and pulse rate) should be collected before the 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 Cohorts 1, 2 and 3 of this study are approximately 545, 440 and 340 mL, respectively. 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

Efficacy parameters are not evaluated in this study.

### 8.3. Safety Assessments

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

### 8.3.1. Physical Examinations

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

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

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

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

Physical examination findings collected during the study will be considered source record 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. When triplicate measurements of supine BP or pulse rate are required per SoA, measurements should be collected 2-4 minutes apart.

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

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

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

#### 8.3.2.2. Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes of rest in a supine position by observing and counting the respirations of the participant for 30 seconds and multiplying by 2. When BP is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before BP measurement.

#### 8.3.2.3. Body Temperature

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

### 8.3.3. Electrocardiograms

Standard 12-lead ECGs will be collected at times specified in the SoA section of this protocol using an ECG system that automatically calculates the HR and measures PR, QT, QTcF, and QRS intervals. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected at -1.0, -0.5, and 0 hours pre-dose on Day 1 of each period will serve as each participant's baseline QTcF value.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any 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 a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

For single ECG collection, 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.

#### 8.3.3.1. Continuous Cardiac Monitoring by Telemetry

All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the CRF. In addition, a printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.

Telemetry should be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the investigator site, or verifiable arrhythmia quantification is required. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing in Period 1. This may be done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the participant is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing.

### 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 14 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.

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

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

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

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

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

#### 8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, 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 intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

#### 8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

#### 8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

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

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

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

### 8.4.2. Method of Detecting AEs and SAEs

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading 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, inhalation, or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then 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 using the CT SAE Report Form and EDP Supplemental Form regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention.

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

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 report 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 report is 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.

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s), 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 4 mL to provide approximately 1.6 mL of plasma, will be collected for measurement of plasma concentrations of PF-06954522 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual times may change but the actual date and time (24-hour clock time) of each sample will be recorded.

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

Samples will be used to evaluate the PK of PF-06954522. Samples collected for analyses of PF-06954522 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. The exploratory results may not be reported in the CSR.

Genetic analyses will not be performed on these PK 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-06954522 will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites may be analyzed with either validated or exploratory methods.

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

Drug concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

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

### 8.6. Genetics

#### 8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

#### 8.6.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

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

### 8.7. Biomarkers

#### 8.7.1. Plasma for Measurement of CCI

Blood samples of approximately 2 mL, to provide a minimum of approximately 0.8 mL plasma, will be collected into appropriately labeled tubes containing $K_2$EDTA for measurement of plasma concentrations of CCI at times specified in the SoA. These samples will be analyzed at the discretion of the sponsor. If analysis of the CCI samples is judged to

be useful, samples from the highest doses may be analyzed first and, if no meaningful effect of PF-06954522 is observed, samples from lower dose groups may not be assayed.

Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual times may change but the actual date and time (24-hour clock time) of each sample will be recorded.

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 collected for analyses of CCI plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. The exploratory results may not be reported in the CSR.

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 CCI will be analyzed using a validated analytical method in compliance with applicable SOPs.

The CCI samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the 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.

CCI concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

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

### 8.7.2. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

- A 2 mL whole blood Prep B2.5 optimized for serum as outlined in the SoA.

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

Retained Research Samples may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

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

### 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 Hypothesis

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

### 9.2. Analysis Sets

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

| Participant Analysis Set | Description |
|---|---|
| Enrolled | "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 to study intervention. |
| Safety analysis set | All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received. |

| Participant Analysis Set | Description |
|---|---|
| PK Concentration Set | All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and in whom at least 1 plasma concentration value is reported. |
| PK Parameter Set | All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention and have at least 1 of the PK parameters of interest calculated. |

### 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. Safety Analyses

All safety analyses will be performed on the safety population (safety analysis set).

AEs, ECGs, BP, pulse rate, respiratory rate, temperature, continuous cardiac monitoring, 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, pulse rate, respiratory rate and temperature abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

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

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

##### 9.3.1.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters HR, QT interval, QTcF, PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

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

**Safety QTcF Assessment**

| Degree of Prolongation | Mild (ms) | Moderate (ms) | Severe (ms) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Absolute value | >450-480 | >480-500 | >500 |
| Increase from baseline | | 30-60 | >60 |

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 ms, but the mean of the triplicates is not >500 ms, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500 ms value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 ms will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 ms. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the pre-dose triplicate values at -1, -0.5, and 0 hours pre-dose on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined. The results of such analyses may not be included in the CSR.

### 9.3.2. PK Analysis

The PK concentration and parameter populations are defined in Section 9.2.

#### 9.3.2.1. Derivation of PF-06954522 PK Parameters

The plasma PK parameters for PF-06954522, following oral dose administration, will be derived from the plasma concentration-time profiles using standard noncompartmental methods as detailed in Table 4, as data permit. Actual PK sampling times will be used in the derivation of PK parameters. If actual PK sampling times are not available, nominal PK sampling times will be used in the derivation of PK parameters.

**Table 4. Plasma PF-06954522 PK Parameters**

| Parameter | Definition | Method of Determination |
|---|---|---|
| $AUC_{last}$ | Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration ($C_{last}$) | Linear/Log trapezoidal method |
| $AUC_{inf}$* | Area under the plasma concentration-time profile from time 0 extrapolated to infinite time | $AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable timepoint estimated from the log-linear regression analysis |
| $C_{max}$ | Maximum plasma concentration | Observed directly from data |
| $T_{max}$ | Time for $C_{max}$ | Observed directly from data as time of first occurrence |
| $t_{½}$* | Terminal elimination half-life | $Log_e(2)/k_{el}$, where $k_{el}$ is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those |

**Table 4. Plasma PF-06954522 PK Parameters**

| Parameter | Definition | Method of Determination |
|---|---|---|
| | | data points judged to describe the terminal log-linear decline will be used in the regression. |
| CL/F * | Apparent clearance | Dose/$AUC_{inf}$ |
| $V_z$/F * | Apparent volume of distribution | Dose/($AUC_{inf}$·$k_{el}$) |
| $AUC_{last}$(dn) | Dose-normalized $AUC_{last}$ | $AUC_{last}$/Dose |
| $AUC_{inf}$(dn)* | Dose-normalized $AUC_{inf}$ | $AUC_{inf}$/Dose |
| $C_{max}$(dn) | Dose-normalized $C_{max}$ | $C_{max}$/Dose |

* As data permits.

### 9.3.2.2. Statistical Methods for PK Data

Plasma concentrations of PF-06954522 will be listed and summarized descriptively by dose (and fasting condition and ethnicity, if appropriate) and nominal PK sampling time. Individual participant and median profiles of the plasma concentration-time data will be plotted by dose (and fasting condition and ethnicity, if appropriate) using actual (for individual) and nominal (for median) times respectively. Median profiles will be presented on both linear and semi-log scales.

The plasma PK parameters will be summarized descriptively by dose (and fasting condition and ethnicity, if appropriate) as applicable. Dose-normalized $AUC_{inf}$, $AUC_{last}$, and $C_{max}$ will be plotted against dose (and fasting condition and ethnicity, if appropriate) using box and whisker plots and will include individual participant values and the geometric means for each dose. These plots will be used to understand the relationship between PK parameters and dose (and fasting condition and ethnicity, if appropriate).

If the food effect is assessed, a mixed effects ANOVA will be performed separately on the natural log transformed $AUC_{inf}$, $AUC_{last}$, and $C_{max}$ (dose-normalized prior to analysis, if appropriate) with fasting condition included as a fixed effect and participant as a random effect. Further details of this analysis will be provided in the SAP.

Additional PK analyses may be performed if deemed appropriate and may not be included in the CSR.

### 9.3.3. Tertiary/Exploratory Endpoint(s) Analysis

The analysis of tertiary/exploratory endpoints will be detailed in the SAP.

### 9.3.4. Other Analyses

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

### 9.4. Interim Analyses

No formal interim analysis will be conducted for this study.

### 9.5. Sample Size Determination

A sufficient number of participants will be screened to achieve approximately 24 participants (up to 3 cohorts of up to approximately 10, 8 and 6 participants in Cohorts 1, 2, and 3, respectively) randomized. This sample size of approximately 24 participants for the entire study has been chosen based on the need to minimize first exposure to humans of a new chemical entity and the requirement to provide adequate safety, tolerability, and PK assessment at each dose level.

In each period of Cohort 1, approximately 8 participants are planned to receive PF-06954522, and 2 participants are planned to receive placebo; with all participants in Cohort 1 at the end of the study having received up to 5 doses of PF-06954522 and up to 2 doses of placebo.

In each period of Cohort 2, approximately 6 participants are planned to receive PF-06954522, and 2 participants are planned to receive placebo; with all participants in Cohort 2 at the end of the study having received up to 4 doses of PF-06954522 and up to 2 doses of placebo.

An optional cohort of Japanese participants (Cohort 3) with a target sample size of approximately 6 participants (approximately 4 receiving PF-06954522, approximately 2 receiving placebo in each period) may also be enrolled, if feasible. The actual number of Japanese participants may be adjusted based on emerging data or operational factors, with a maximum sample size of up to 8 participants (6 receiving PF-06954522 and 2 receiving placebo in each period).

# 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. Financial Disclosure

Not applicable.

### 10.1.3. 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 their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date 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.

#### 10.1.3.1. Electronic Consent

Participants may be able to experience the informed consent process by electronic means (eConsent). The eConsent process includes an electronic presentation of the informed consent document (eICD), clinical trial educational components (as applicable), and electronic signatures (if allowed by local regulations). The use of eConsent does not replace or alter the ICD content or informed consent process as described above. The eConsent process complies with applicable regulations and sponsor policies to ensure reliability and data privacy.

### 10.1.4. Data Protection

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

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

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to 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 SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

### 10.1.5. Committees Structure

#### 10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

### 10.1.6. 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 18 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.

### 10.1.7. 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 records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and IQMP maintained and utilized by the sponsor or designee.

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

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

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

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly

provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

### 10.1.8. Source Documents

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

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

Definition of what constitutes a source document 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 record) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring 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.

### 10.1.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

### 10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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 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.

### 10.1.11. Publication Policy

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.

### 10.1.12. 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 clinical trial management system.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study 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; for example: calculation of estimated kidney function (ie, 2021 CKD-EPI eGFR as standard lab safety test). 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 Assessments**

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hemoglobin | BUN | Local dipstick[g]: | FSH[e,f] |
| Hematocrit | Creatinine | pH | HBcAb[f] |
| RBC count | Cystatin C[a] | Glucose (qual) | HBsAb[f] |
| MCV, MCH, MCHC | eGFR[b] | Protein (qual) | HBsAg[f] |
| Platelet count | Glucose (fasting) | Blood (qual) | HCVAb[f] |
| WBC count | Calcium | Ketones | HIV[f] |
| Total neutrophils (Abs) | Sodium | Nitrites | HbA1c[f] |
| Eosinophils (Abs) | Potassium | Leukocyte esterase | TSH[f] |
| Monocytes (Abs) | Chloride | Urobilinogen | |
| Basophils (Abs) | Total $CO_2$ (bicarbonate) | Urine bilirubin | Urine albumin to creatinine ratio (quantitative)[f,h] |
| Lymphocytes (Abs) | AST, ALT | | |
| | Total bilirubin | Laboratory: | |
| | Direct and indirect bilirubin[c] | Microscopy and culture[d] | Urine drug screen[i] |
| | GGT | | |
| | Alkaline phosphatase | | Calcitonin[j] |
| | Creatine Kinase (CK) | | Amylase[j] |
| | Uric acid | | Lipase[j] |
| | Albumin | | Total bile acids[j] |
| | Total protein | | |

a. Serum Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase is observed (see Section 7.1.1).
b. Screening and Baseline eGFR is measured with Screat-based formula. Age-specific kidney function calculation (see Section 10.7.2) is recommended to assess presence or absence of post-baseline change in kidney function.
c. Test as reflex if total bilirubin is elevated.
d. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
e. For confirmation of postmenopausal status only in females <60 years old and not using hormonal or HRT only.
f. At screening only.
g. Assessed by urine dipstick.
h. Assessed by urine sample biochemical analysis.
i. At screening and upon admission for each inpatient stay. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site- and study-specific).
j. Review of these data is not required prior to dosing and dose escalation in each period; cumulative results will be reviewed as they become available.

**Table 6. Protocol-Required Laboratory Assessments – Reflex Testing**

| Hematology | Chemistry | Urinalysis on Site | Other |
|---|---|---|---|
| If Hb/RBC abnormal:<br>MCV, MCH, MCHC<br>Neutrophils (%)<br>Eosinophils (%)<br>Basophils (%)<br>Lymphocytes (%)<br>Monocytes (%)<br>RBC morphology<br>RBC distribution width | **Required:**<br>For suspected DILI:<br>AST/ALT<br>T bili, albumin, CK, direct and indirect bili<br>GGT, PT/INR, eosinophils (%), alkaline phosphatase<br><br>The following additional testing may be warranted:<br>Acetaminophen/paracetamol or<br>protein adduct levels<br>Hepatitis serology (even if screening negative)<br>Total bile acids<br>Liver imaging<br><br>For suspected DICI/DIKI:<br>Creatinine (Screat)<br>Cystatin C[a] (Scys)<br>eGFR (Screat only and combined Screat+Scys)[b]<br><br>Urine albumin-to-creatinine-ratio (UACR) | **Local Laboratory**<br>Microscopy and culture for positive local dipstick tests[c] | Hepatitis B DNA<br>Hepatitis C RNA |

a. Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if clinically-relevant serum creatinine increase post-baseline is observed (see Section 7.1.1).
b. Creatinine (Screat): Screening and Baseline eGFR is measured with Screat-based formula. Age-specific kidney function calculation (see Section 10.7.2) is recommended to assess the presence or absence of post-baseline change in kidney function.
c. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both. Any positive results are to be reported as an AE.

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.

Laboratory/analyte results that could unblind the study and have been collected for the purpose of the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

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

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

### 10.3.1. Definition of AE

| AE Definition |
| --- |
| • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.<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 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**<br><br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br><br>• 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**<br><br>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:**<br><br>• 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.<br><br>• 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 using 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.

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>**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 SAE): is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental 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. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

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

**Follow--up of AEs and SAEs**

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

- New or updated information will be recorded in the originally 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 (eg, eSAE or PSSA).
- If the electronic system is unavailable, then the site will use the paper SAE report form (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 one of the methods 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

Male participants are eligible to participate if they agree to the following requirements 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 reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom, and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak when having sexual intercourse with a WOCBP who is not currently pregnant.

  - In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

### 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 (a) is not pregnant or breastfeeding; and (b) agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for at least 28 days after last dose of study intervention; and (c) Is not a WOCBP (see definition in Section 10.4.3).

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 or oligomenorrhea) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to 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.

3. Postmenopausal female.

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

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

        - 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 male participants or their female partners who are of childbearing potential should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods for male participants or their female partners who are of childbearing potential are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

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

    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*

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

    - Oral + barrier*
    - Injectable + barrier*

8. Sexual Abstinence

    Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated

with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

* Acceptable barrier methods to be used concomitantly with options 6 or 7 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).

## 10.5. Appendix 5: Genetics

**Use/Analysis of DNA**

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

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

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

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

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

- The samples will be retained as indicated:

- Retained samples will be stored indefinitely or for another period as per local requirements.

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

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

## 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, eosinophils (%), 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, total bile acids, 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 Screat measurement to estimate kidney function [eg, Screat-based eGFR]. Obtaining Screening or Baseline Scys and postbaseline reflex Scys (if confirmed Screat increase ≥0.3 mg/dL) makes it feasible to distinguish AKI from DICI. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated:

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat only-based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat only-based equation (see Section 10.7.2.1) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat only-based eGFR and combined Screat plus Scys eGFR).

### 10.7.2. Age-Specific Kidney Function Calculation Recommendations

#### 10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

eGFR (mL/min/1.73m²)[17]

| **2021 CKD-EPI Screat Only** | **Screat** *(mg/dL)* | **Scys** *(mg/L)* | **Recommended eGFR Equation** |
|---|---|---|---|
| Female | if ≤ 0.7 | NA | $eGFR = 143 \times (Screat/0.7)^{-0.241} \times (0.9938)^{Age}$ |
| Female | if > 0.7 | NA | $eGFR = 143 \times (Screat/0.7)^{-1.200} \times (0.9938)^{Age}$ |
| Male | if ≤ 0.9 | NA | $eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$ |
| Male | if > 0.9 | NA | $eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$ |
| **2021 CKD-EPI Screat-Scys Combined** | **Screat** *(mg/dL)* | **Scys** *(mg/L)* | **Recommended eGFR Equation** |
| Female | if ≤ 0.7 | if ≤ 0.8 | $eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$ |
| Female | if ≤ 0.7 | if > 0.8 | $eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$ |
| Female | if > 0.7 | if ≤ 0.8 | $eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$ |
| Female | if > 0.7 | if > 0.8 | $eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$ |
| Male | if ≤ 0.9 | if ≤ 0.8 | $eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$ |
| Male | if ≤ 0.9 | if > 0.8 | $eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$ |
| Male | if > 0.9 | if ≤ 0.8 | $eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$ |
| Male | if > 0.9 | if > 0.8 | $eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$ |

### 10.7.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age appropriate formulae (see Section 10.7.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

### 10.7.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function will be according to CTCAE criteria.

| **CTCAE Term (2017)** | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| **AKI** | NA | NA | Hospitalization indicated | Life-threatening consequences; dialysis indicated | Death |
| AKI: A disorder characterized by acute loss of kidney function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidneys), renal (kidney damage), or post-renal causes (ureteral or bladder outflow obstruction. | | | | | |
| **Creatinine increased** | >ULN to 1.5 × ULN | >1.5 to 3.0 × baseline OR >1.5 to 3.0 × ULN | >3.0 to 6.0 × baseline OR >3.0 to 6.0 × ULN | >6.0 × ULN | NA |
| **CKD** | eGFR ≥60 to 89 mL/min/1.73m² OR eCrCl ≥60 to 80 mL/min | eGFR 30 to 59 mL/min/1.73m² OR eCrCl 30 to 59 mL/min | eGFR 15 to 29 mL/min/1.73m² OR eCrCl 15 to 29 mL/min | eGFR <15 mL/min/1.73m² OR eCrCl <15 mL/min OR dialysis indicated | Death |
| **Proteinuria** | ADULTS: Proteinuria 1+ OR Proteinuria >0.5 to <1.0 g/24 h | ADULTS: Proteinuria 2+ or 3+ OR Proteinuria 1.0 to <3.5 g/24 h | ADULTS: Proteinuria 4+ OR Proteinuria ≥3.5 g/24 h | NA | NA |
| CKD: A disorder characterized by gradual and usually permanent loss of kidney function resulting in kidney failure. | | | | | |

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

| ECG Findings That May Qualify as AEs |
|---|
| • Marked sinus bradycardia (rate <40 bpm) lasting minutes.<br>• New PR interval prolongation >280 ms.<br>• New prolongation of QTcF to >480 ms (absolute).<br>• New prolongation of QTcF by >60 ms from baseline.<br>• New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.<br>• New-onset type I second-degree (Wenckebach) AV block of >30-second duration.<br>• Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes. |
| **ECG Findings That May Qualify as SAEs** |
| • QTcF prolongation >500 ms.<br>• Absolute value of QTcF > 450 ms AND QTcF change from baseline >60 ms.<br>• New ST-T changes suggestive of myocardial ischemia.<br>• New-onset LBBB (QRS complex>120 ms).<br>• New-onset right bundle branch block (QRS complex>120 ms).<br>• Symptomatic bradycardia.<br>• Asystole<br>  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;<br>  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.<br>• 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 major events of potential clinical concern listed above 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 is to reported as AEs/SAEs.

## 10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below should not be taken with PF-06954522 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), if the overall benefit:risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial

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.

CCI

## 10.10. Appendix 10: Abbreviations

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

| Abbreviation | Term |
|---|---|
| A1 to A3 | albuminuria (KDIGO albuminuria severity standardization) |
| Abs | absolute |
| ADL | activity/activities of daily living |
| AE | adverse event |
| AESI | adverse event of special interest |
| CCI | [redacted] |
| AKI | acute kidney injury |
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| $AUC_{24}$ | area under the concentration-time curve from time 0 to 24 hours |
| $AUC_{inf}$ | area under the concentration-time curve from time 0 to infinity |
| $AUC_{inf}(dn)$ | dose-normalized $AUC_{inf}$ |
| $AUC_{last}$ | area under the concentration-time curve from 0 to time of last measurable concentration |
| $AUC_{last}(dn)$ | dose-normalized $AUC_{last}$ |
| AV | atrioventricular |
| AxMP | auxiliary medicinal product |
| BA | bioavailability |
| BBS | Biospecimen Banking System |
| CCI | [redacted] |
| BE | bioequivalence |
| BMI | body mass index |
| BP | blood pressure |
| bpm | beats per minute |
| BUN | blood urea nitrogen |
| CCI | [redacted] |
| $C_{eff}$ | steady state efficacious concentration |
| CFR | Code of Federal Regulations |
| CIOMS | Council for International Organizations of Medical Sciences |
| CK | creatine kinase |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CL | total clearance of drug from eg, plasma |
| CL/F | apparent clearance of drug from eg, plasma |
| $CL_p$ | plasma clearance |
| $C_{max}$ | maximum observed concentration |
| $C_{max}(dn)$ | dose-normalized $C_{max}$ |
| $CO_2$ | carbon dioxide (bicarbonate) |

| Abbreviation | Term |
|---|---|
| COVID-19 | coronavirus disease 2019 |
| CCI | |
| CRF | case report form |
| CRO | contract research organization |
| CRU | clinical research unit |
| CSR | Clinical Study Report |
| CT | clinical trial |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| CV | cardiovascular |
| CCI | |
| DCT | data collection tool |
| DDI | drug-drug interaction |
| DICI | drug-induced creatinine increase |
| DIKI | drug-induced kidney injury |
| DILI | drug-induced liver injury |
| DNA | deoxyribonucleic acid |
| DU | dispensable unit |
| EC | ethics committee |
| ECC | emergency contact card |
| ECG | electrocardiogram or electrocardiography |
| CCI | |
| eCrCl | estimated creatinine clearance |
| eCRF | electronic case report form |
| EDB | exposure during breastfeeding |
| E-DMC | External Data Monitoring Committee |
| EDP | exposure during pregnancy |
| EDR | extemporaneous dispensing record |
| eGFR | estimated glomerular filtration rate |
| EGFR | epidermal growth factor receptor |
| eICD | electronic informed consent document |
| EMA | European Medicines Agency |
| ET | end of treatment |
| eSAE | electronic serious adverse event |
| ESR | erythrocyte sedimentation rate |
| EU | European Union |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database) |
| FDA | Food and Drug Administration |
| FIH | first in human |
| FSH | follicle-stimulating hormone |
| CCI | |
| F/U | follow-up |

| Abbreviation | Term |
|---|---|
| G1 to G5 | Grade (KDIGO eGFR category standardization) |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GLP-1 | glucagon-like peptide-1 |
| GLP-1R | glucagon-like peptide-1 receptor |
| GLP-1RA | glucagon-like peptide-1 receptor agonist |
| HbA1c | glycated hemoglobin |
| 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 |
| ICD | informed consent document |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ID | identification |
| IMP | investigational medicinal product |
| IND | Investigational New Drug |
| INR | international normalized ratio |
| IPAL | Investigational Product Accountability Log |
| CCI | |
| IPM | investigational product manual |
| IQMP | integrated quality management plan |
| IRB | Institutional Review Board |
| IRC | internal review committee |
| IRT | Interactive Response Technology |
| ISO | International Organization for Standardization |
| IV | Intravenous(ly) |
| IWR | Interactive Web Response |
| K | Proportionality constant for Schwartz Equations (kidney function) |
| $K_2$EDTA | dipotassium ethylenediaminetetraacetic acid |
| $k_{el}$ | first-order elimination rate constant |
| KDIGO | Kidney Disease Improving Global Outcomes |
| CCI | |
| LBBB | left bundle branch block |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| LPD | local product document |
| CCI | |

| Abbreviation | Term |
|---|---|
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MEN2 | multiple endocrine neoplasia syndrome type 2 |
| CCI | |
| MQI | medically qualified individual |
| MTC | medullary thyroid carcinoma |
| NA | not applicable |
| NHP | nonhuman primate |
| NIMP | noninvestigational medicinal product |
| NOAEL | no observed adverse effect level |
| CCI | |
| Pbo | placebo |
| CCI | |
| PCR | polymerase chain reaction |
| PCRU | Pfizer Clinical Research Unit |
| PD | pharmacodynamic(s) |
| PE | physical examination |
| CCI | |
| PGx | pharmacogenomic(s) |
| PI | principal investigator |
| PIB | powder in bottle |
| PK | pharmacokinetic(s) |
| PSSA | Pfizer's Serious Adverse Event Submission Assistant |
| PT | prothrombin time |
| PTA | post-trial access |
| PTH | parathormone |
| PVC | premature ventricular contraction/complex |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QTc corrected using Fridericia's formula |
| QTL | quality tolerance limit |
| qual | qualitative |
| RBC | red blood cell |
| RNA | ribonucleic acid |
| SADE | serious adverse device effect |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | subcutaneous |
| SCL | supply chain lead |
| Scr | serum creatinine |
| Screat | serum creatinine |

| Abbreviation | Term |
|---|---|
| Scys | serum cystatin C |
| SoA | schedule of activities |
| SOP | standard operating procedure |
| SRSD | Single Reference Safety Document |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| $t_{½}$ | terminal phase half-life |
| T2DM | type 2 diabetes mellitus |
| T3 | total triiodothyronine |
| T4 | thyroxine |
| TB | tuberculosis |
| TBD | to be determined |
| T bili | total bilirubin |
| $T_{max}$ | Time for $C_{max}$ |
| THC | tetrahydrocannabinol |
| TOC | table of contents |
| TSH | thyroid-stimulating hormone |
| UACR | urine albumin/creatinine ratio |
| ULN | upper limit of normal |
| CCI | [redacted] |
| US | United States |
| USPI | United States Prescribing Information |
| UTI | urinary tract infection |
| $V_{ss}$ | steady-state volume of distribution |
| $V_z/F$ | apparent volume of distribution for extravascular dosing |
| WBC | white blood cell |
| WOCBP | woman/women of childbearing potential |

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