A PHASE 1, OPEN-LABEL, PARALLEL-GROUP, SINGLE-DOSE STUDY IN HEALTHY ADULT MALE PARTICIPANTS TO INVESTIGATE THE ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION OF [^{14}C]-PF-07220060 AND TO ASSESS THE ABSOLUTE BIOAVAILABILITY AND FRACTION ABSORBED OF PF-07220060 USING A ^{14}C-MICROTRACER APPROACH

Study Intervention Number:	PF-07220060
Study Intervention Name:	NA
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Pediatric Investigational Plan Number:	NA
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Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: ADME: A Study to Understand What the Body does to the Study Compound Called PF-07220060 When Taken by Healthy Adults.

Document History

Document	Version Date
Amendment 1	06 December 2023
Original protocol	13 October 2023

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any global protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 1 (06 December 2023)

Overall Rationale for the Amendment:

This amendment is to address the regulatory requests from Netherlands MREC Part 1 RFIs dated on 29 November 2023. Please refer to the following table for the changes.

Description of Change	Brief Rationale	Section # and Name
	Non-substantial Modifications	
To add **reticulocyte count** to Hematology tests in Table 5 Protocol-Required Laboratory Assessments	To fulfill the regulatory request from NL MREC Part 1 RFI dated on 29 November 2023	Appendix 2 Clinical Laboratory Tests
To clarify the study is a parallel-cohort study **including 2 independent cohorts without crossover**. Cohorts 1 and 2 are enrolled sequentially with 15 days difference.	To fulfill the regulatory request from NL MREC part 1 RFI dated on 29 November 2023	Section 1.1 Synopsis; Section 4.2 Scientific Rationale for Study Design
To clarify that randomization in the text refers to allocation (number), as the study is not a randomized study.	To fulfill the regulatory request from NL MREC part 1 RFI dated on 29 November 2023	Section 1.1 Synopsis; Section 4.1 Overall Design; Section 6.3 Assignment to Study Intervention; Section 9.2 Analysis Sets
General editorial changes	To correct some typos, and make minor edits for consistency	Throughout the protocol

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Open-Label, Parallel-Group, Single-Dose Study in Healthy Adult Male Participants to Investigate the Absorption, Distribution, Metabolism and Excretion of ^{14}C-PF-07220060 and to Assess the Absolute Bioavailability and Fraction Absorbed of PF-07220060 Using a ^{14}C-Microtracer Approach

Brief Title: ADME: A Study to Understand What the Body does to the Study Compound Called PF-07220060 When Taken by Healthy Adults.

Regulatory Agency Identification Number(s):

US IND Number:	145,814
EU CT Number:	2023-507074-40-00
ClinicalTrials.gov ID:	Not Applicable
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	C4391010
Phase:	1

Rationale:

PF-07220060 is a selective cyclin-dependent kinase (CDK)4 inhibitor that is currently being investigated in participants with metastatic or advanced solid tumors. PF-07220060 differs from currently approved dual CDK4/6 inhibitors in that it displays greater CDK4-over-CDK6 selectivity and is therefore hypothesized to drive tumor growth inhibition through greater CDK4 selectivity, while minimizing CDK6 driven hematopoetic effects. This may translate to improved efficacy and tolerability over other CDK4/6 inhibitors.

The purpose of the study will be to investigate the metabolism and excretion following a single oral administration of [^{14}C]PF-07220060 under fasted condition in healthy male participants. The data generated from this study will be used to assess clearance mechanisms for PF-07220060 as well as identify metabolites that should be qualified to adhere to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (M3) R2 guidance. In addition, this study will characterize the fraction of dose absorbed and bioavailability of orally administered PF-07220060 under the fasted condition, in reference to an intravenous (IV) infusion of [^{14}C]PF-07220060 (given as a microtracer microdose infusion following administration of an oral unlabelled dose), and will also assess pharmacokinetic (PK) parameters of PF-07220060 following both oral and IV administration of [^{14}C]PF-07220060.

This study will also evaluate sensory and taste attributes (eg, bitterness and tongue/mouth sensation) of the PF-07220060 oral suspension to guide the future development of pediatric-friendly oral formulations.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the rate and extent of excretion of total radioactivity following administration of a single oral dose of [^{14}C]PF-07220060.	• Mass Balance: Cumulative recovery (%) of radioactivity in urine and feces (adjusted for vomitus, if any), expressed as a percent of total oral radioactive dose administered (quantification by AMS).
• To characterize the metabolic profile for PF-07220060 and identify the circulating and excreted metabolites of PF-07220060 following administration of a single oral dose of [^{14}C]PF-07220060.	• Metabolic profiling/metabolite identification and determination of relative abundance of [^{14}C]PF-07220060 and its metabolites in plasma, urine and feces, if possible (Cohort 1).
Secondary:	**Secondary:**
• To determine the absolute oral bioavailability (F) of PF-07220060 from a single oral dose of PF-07220060 under fasted conditions followed by a single IV microdose of [^{14}C]PF-07220060.	• The ratio of dose-normalized plasma AUC_{inf} of oral PF-07220060 (LCMS) and IV [^{14}C]PF-07220060 (HPLC-AMS) [Cohort 2 only].
• To determine the fraction of PF-07220060 dose absorbed (F_a) from a single oral dose of [^{14}C]PF-07220060 under fasted conditions.	• F_a calculated from the ratio of total recovered radioactivity [^{14}C] in urine following single dose administration of [^{14}C]PF-07220060 orally in Cohort 1 and via IV infusion in Cohort 2 (quantification by AMS).
• To determine the safety and tolerability of PF-07220060, administered as a single oral dose of [^{14}C]PF-07220060 or a single oral dose of PF-07220060 followed by administration of a single IV dose of [^{14}C]PF-07220060.	• AE monitoring, physical examination, clinical laboratory measurements, vital signs and 12-lead ECGs.

Abbreviations: AE = adverse event; AMS = accelerator mass spectrometry; AUC_{inf} = area under the plasma concentration time profile from time 0 extrapolated to infinite time; ECG = electrocardiogram; F = oral bioavailability; F_a = fraction absorbed; HPLC = high performance liquid chromatography; IV = intravenous(ly); LCMS = liquid chromatography mass spectrometry.

Overall Design:

This study will be a Phase 1, open-label, parallel-group, single-dose study of PF-07220060 to characterize the metabolic profile and routes of excretion for oral [^{14}C]PF-07220060 and to evaluate the absolute oral bioavailability (F) of PF-07220060 and fraction absorbed (F_a) of [^{14}C]PF-07220060, in reference to IV microtracer [^{14}C]PF-07220060 in fasted healthy male participants.

Number of Participants:

Approximately 6 healthy adult male participants will be enrolled in each of the 2 cohorts. Definition of "evaluable participants" will be provided in the Statistical Analysis Plan (SAP).

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 screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

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

2. Body mass index (BMI) of 17.5-30.5 kg/m^2; and a total body weight >50 kg (110 lb).

3. Evidence of a personally signed and dated informed consent document (ICD) indicating that the participant has been informed of all pertinent aspects of the study.

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

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 human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HBsAg), or hepatitis C antibody (HCVAb). Hepatitis B vaccination is allowed.

2. Participants with a history of irregular bowel movements (eg, regular episodes of diarrhea or constipation, irritable bowel syndrome [IBS] or lactose intolerance).

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 single oral dose of study intervention.

   - Concomitant use of any medications or substances that are strong inducers or inhibitors of cytochrome P450 (CYP) 3A4 or uridine diphosphase-glucuronosyltransferase (UGT) 2B7 are prohibited within 5 half-lives plus 14 days (up to 28 days) prior to the single oral dose of PF-07220060.

   - Use of proton-pump inhibitors is prohibited from 28 days prior to the first dosing of study intervention, and through the study. Other acid reducing agents including H2-receptor antagonists or local antacids should not be used for at least 7 days or 5 half-lives, whichever is longer, before the first dosing of study intervention and are prohibited through 5 days after the dosing.

5. Participants unwilling or unable to use a required concomitant medication(s).

6. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives (whichever is longer) preceding the first dose of study intervention used in this study. Previous exposure to PF-07220060 or participation in studies requiring PF-07220060 administration.

7. Participants enrolled in a previous radionucleotide study or who have received radiotherapy within 12 months prior to screening or such that total radioactivity would exceed acceptable dosimetry.

8. A positive urine drug test. A single repeat for positive drug screen may be allowed.

9. 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 BP is ≥140 mm Hg (systolic) or 150 mm Hg (based on age) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

10. Standard 12-lead electrocardiogram (ECG) that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTc corrected using Fridericia's formula [QTcF] >450 ms, complete left bundle branch block [LBBB], signs of an acute or indeterminate- age myocardial infarction, ST segment and T wave [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 is used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

11. Total ^{14}C radioactivity measured in plasma exceeding 11 mBq/mL.

12. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the studyspecific 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 a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;
    - Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 based on the 2021 chronic kidney disease epidemiology (CKD-EPI) (combined serum creatinine plus serum cystatin C) equation;
    - Blood calcium or potassium <0.9 × lower limit of normal (LLN) or >1.1 × ULN;
    - Absolute neutrophil count <0.8 × LLN.

13. 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) 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).

14. Use of tobacco or nicotine containing products within 3 months of screening or a positive urine cotinine test (ie, active smokers and those who currently use nicotine-containing products are excluded from participation in this study).

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

16. History of sensitivity to heparin or heparin-induced thrombocytopenia.

17. Participants whose occupation requires exposure to radiation or monitoring of radiation exposure.

18. 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:

Study Intervention(s)			
Intervention Name	[^{14}C]PF-07220060	PF-07220060	[^{14}C]PF-07220060
Type	Drug	Drug	Drug
Use	Experimental	Experimental	Experimental
IMP or AxMP	IMP	IMP	IMP
Dose Formulation	Oral suspension	Oral suspension	IV solution
Unit Dose Strength(s)	100 mg	100 mg	CCI µg
Dosage Level(s)	100 mg, single dose	100 mg, single dose	CCI µg, single dose
Route of Administration	Oral	Oral	IV infusion

Study Arm(s)		
Arm Title	Cohort 1	Cohort 2
Arm Type	Experimental	Experimental
Arm Description	Oral dose of 100 mg PF-07220060 containing CCI nCi [^{14}C] ([^{14}C]PF-07220060) will be administered as an extemporaneously prepared liquid formulation.	Unlabeled oral dose of PF-07220060, 100 mg will be administered as an extemporaneously prepared liquid formulation. Approximately 2 hours after the administration of the unlabeled oral dose, a single dose of CCI µg PF-07220060 containing CCI nCi [^{14}C] ([^{14}C]PF-07220060) will be administered IV, as an infusion over approximately 30 minutes
Associated Intervention Labels	[^{14}C]PF-07220060	PF-07220060, [^{14}C]PF-07220060

This will be a parallel-cohort study including 2 independent cohorts without crossover. Cohort 2 will be enrolled approximately 15 days after Cohort 1 enrollment. Eligible participants will be admitted to the clinical research unit (CRU) on Day -1. In **Cohort 1**, participants will receive a single oral dose of 100 mg [^{14}C]PF-07220060 containing approximately CCI nCi on Day 1. Blood, urine, feces, and vomitus (if any) will be collected over predefined intervals. Participants dosed in Cohort 1 will be eligible for discharge between Days 5 to 14 when at least one of the 3 following criteria are met: (1) ≥90% of the administered radioactive dose has been recovered in urine+feces+vomitus (if any); (2) <1%

of the administered radioactive dose has been recovered in urine+feces during 24-hour intervals over 2 consecutive days, OR (3) the participant has reached Day 14. In **Cohort 2**, participants will receive a single oral 100 mg dose of unlabeled PF-07220060 on Day 1. At approximately 2 hours after oral dose, a single IV dose of CCI µg (microdose) [^{14}C]PF-07220060 containing approximately CCI nCi will be administered as an infusion over 30 minutes. Blood, urine, feces, and vomitus (if any) samples will be collected as per detailed in the schedule of activities (SoA) up until the discharge day occurring between Days 5 to 14. The duration of confinement for Cohort 2 participants will equal the longest individual participants duration of confinement in Cohort 1 so that the duration of urine sample collections over the periods is consistent to aid in accurate estimation of the F_a.

Statistical Methods:

Approximately 6 healthy adult male participants will be enrolled in each of the 2 cohorts based on the industry standard sample size for mass balance and radiolabeled microtracer studies. This sample size was not chosen based on any empirical data or hypothesis testing criteria.

- **Mass Balance**: Percent recovery of administered radioactivity excreted at each time interval and total radioactivity recovery in urine and feces (adjusted for vomitus, if any) will be reported.

- **Mean Absolute Oral bioavailability (F)** will be estimated as the ratio of geometric means of dose-normalized AUC_{inf} (area under the concentration-time profile from time 0 to infinity) for oral unlabeled PF-07220060 versus IV radiolabeled PF-07220060 (from Cohort 2 only).

- **Mean Fraction Absorbed (F_a)** will generally be estimated as the ratio of total radioactivity (dose normalized) excreted into the urine (from time 0 to the time of last measurable concentration) following oral and IV administration of [^{14}C]PF-07220060 microtracer doses in Cohorts 1 and 2, respectively.

- **Metabolic Profiling and Metabolite Identification**: Major metabolites of PF-07220060 in plasma, urine, and feces will be identified, if possible. Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the clinical study report (CSR).

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

Pharmacokinetics Analysis

- Mass balance will be determined by cumulative recovery (%) of radioactivity in urine, feces and vomitus (if any).
- The PK concentration population is defined as all participants allocated and treated who have at least 1 PF-07220060, [^{14}C]PF-07220060, or ^{14}C total radioactivity concentration in the whole treatment period.
- The PK parameter analysis population is defined as all participants allocated and treated who have at least 1 of the PF-07220060, [^{14}C]PF-07220060, or ^{14}C total radioactivity PK parameters of primary interest in the whole treatment period.
- PK parameters for PF-07220060 will be analyzed using standard noncompartmental methods of analysis. Actual PK sampling times will be used in the derivation of PF-07220060 PK parameters when available, otherwise nominal times will be used.

Ethical Considerations:

PF-07220060 will not provide any clinical benefit to healthy participants in this study. This study is designed primarily to assess human PK, absorption, metabolism, and elimination of PF-07220060. Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. A single 100 mg oral dose of PF-07220060 (Cohort 1), and a single 100 mg oral dose followed by CCI µg IV dose of PF-07220060 (Cohort 2) are anticipated to be safe and well tolerated. Taking into account the measures to minimize risk to participants, the potential risks associated with PF-07220060 are justified by the anticipated benefits that may be afforded by furthering the understanding of PF-07220060.

1.2. Schema

Not applicable

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Table 1. Schedule of Activity (Cohort 1-Oral [^{14}C]-PF-07220060 Administration)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screen[a]		Study Period															FU phone call	Early Termination/ Discontinuation
Days relative to Day 1	**Days (-28 to -2)**	**Day -1**	**Day 1**										**Day 2**		**Day 3**	**Day 4**	**Day 5-14[b]**	**Day 29-36**	
Hours After Oral [^{14}C]-PF-07220060 Dose	-	-	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	**72**	**96-312**	-	-
Informed consent	X																		
Review of eligibility criteria	X	X																	
Inpatient stay at CRU		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X[b]		X
Medical history	X	X																	
Demography[c]	X																		
Review drug, alcohol/tobacco use[d]	X	X															X[e]	X	X
Review prior and concomitant medications	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Physical examination[f]	X	X															X[e]		X
Supine 12-lead ECG (single)	X		X					X									X[e]		X

Table 1. Schedule of Activity (Cohort 1-Oral [^{14}C]-PF-07220060 Administration)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screen[a]		Study Period															FU phone call	Early Termination/ Discontinuation
Days relative to Day 1	**Days (-28 to -2)**	**Day -1**	**Day 1**										**Day 2**		**Day 3**	**Day 4**	**Day 5-14[b]**	**Day 29-36**	
Hours After Oral [^{14}C]-PF-07220060 Dose	-	-	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	**72**	**96-312**	-	-
Supine vital signs (blood pressure and pulse rate)	X		X					X									X[e]		X
Contraception Check[g]	X	X																X	X
Serious and non-serious adverse event monitoring	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Oral [^{14}C]-PF-07220060 administration[h]			X																
Taste assessment[i]			X[i]																
Emesis collection for radioactivity measurement, if occurs[j]			X	→	→	→	→	→	→	→	→	→	X	→	X	X			
Blood Samples																			
PK of PF-07220060 [LCMS]/Total ^{14}C radioactivity[k]	X[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]		X
Metabolite identification[m]			X	X	X	X		X	X	X	X		X		X	X	X[b,m]		X
Clinical laboratory after ≥4 hour fast	X	X													X		X[e]		X
Serology: HBsAg, HbsAb, HbcAb, HCVAb, and HIV[n]	X																		

Table 1. Schedule of Activity (Cohort 1-Oral [^{14}C]-PF-07220060 Administration)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screen[a]		Study Period															FU phone call	Early Termination/ Discontinuation
Days relative to Day 1	**Days (-28 to -2)**	**Day -1**	**Day 1**										**Day 2**		**Day 3**	**Day 4**	**Day 5-14[b]**	**Day 29-36**	
Hours After Oral [^{14}C]-PF-07220060 Dose	-	-	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	**72**	**96-312**	-	-
Research Sample for Pharmacogenomics[o]			X[o]																
Urine samples for																			
Drug test[p]	X	X																	
Cotinine test[p]	X	X																	
Spot collection for urinalysis (and microscopy, if needed)	X	X											X				X[e]		X
PK of PF-07220060 [LCMS]/Total ^{14}C radioactivity/Metabolite identification[q]		X	X	→	→	→	→	→	→	→	X	→	X	→	X	X	X		
Feces samples for																			
Total ^{14}C radioactivity/Metabolite identification[r]		X	X	→	→	→	→	→	→	→	→	→	X	→	X	X	X		

a. Screening will be performed within 28 days prior to the single oral dose of PF-07220060.
b. See Section 4.1 for details on Cohort 1 discharge criteria.
c. Demographics will include participant race, ethnicity, age, gender, height, and weight during the screening visit.
d. The review of drug, alcohol/tobacco use may include an alcohol breath test or urine alcohol test or blood alcohol test (at discretion of investigator), which will be performed at screening, on Day -1 and at discharge. These tests may be performed at any other time at the discretion of the investigator.
e. Procedures to be performed only on the day of discharge or Day 14. No ECG or vital signs will be collected on Day 14. (see also Section 4.1).
f. Complete physical exam including height and weight will be performed by trained medical personnel at the CRU at screening or Day -1 only. A brief physical examination may be performed prior to discharge from the CRU and at other designated time points at the discretion of the investigator.
g. The investigator or his/her designee will discuss with the participant the need to use highly effective contraception consistently and correctly according to contraception guidelines.

Table 1. Schedule of Activity (Cohort 1-Oral [^{14}C]-PF-07220060 Administration)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screen[a]		Study Period															FU phone call	Early Termination/ Discontinuation
Days relative to Day 1	Days (-28 to -2)	Day -1	Day 1										Day 2		Day 3	Day 4	Day 5-14[b]	Day 29-36	
Hours After Oral [^{14}C]-PF-07220060 Dose	-	-	0	0.5	1	2	3	4	6	8	12	16	24	36	48	72	96-312	-	-

h. PF-07220060 will be administered orally after overnight fasting of at least 10 hours on Day 1.
i. Questionnaire to be completed by participants as soon as practically possible (within 1 min) after completion of dosing, *plus* at 5 min, 10 min, and 20 min post dose. PK samples will take the priority when the 2 procedures conflict.
j. Vomitus samples will be collected as described in Section 8.5.3.
k. Blood samples will be collected at predose (within approximately 1 hour prior to PF-07220060 dosing) and at post-dose time points indicated in the table up to discharge. If ECG and blood pressure/pulse rate assessments are scheduled at the same nominal time point as a PK sample, PK samples should be collected after completion of these assessments, with blood sampling for PK as close as possible to the planned timepoint. Blood samples will be processed to plasma as per instructions of the lab manual. (See also Section 8.5.1).
l. This 8 mL screening sample collection will not be used to analyze the cold PF-07220060 but will be used to assess ^{14}C total radioactivity for screening and be stored for potential use as the diluent for post-dose AMS samples.
m. Blood samples (approximately 10 mL) will be collected at predose (within approximately 1 hour prior to PF-07220060 dosing) and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 144 (if still in CRU) hours post-dose. If ECG and blood pressure/pulse rate assessments are scheduled at the same nominal time point as these samples, these samples should be collected after completion of these assessments, with blood sampling for PK as close as possible to the planned timepoint. Blood samples will be processed to plasma as per instructions of the lab manual. (See also Section 8.5.1).
n. HbsAb will be tested if HbsAg and/or HbcAb are positive.
o. 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.
p. Urine drug and urine cotinine (mandatory) and alcohol breath test or urine alcohol test or blood alcohol test (at discretion of investigator) will be performed at screening, on Day -1. These tests may be performed at any other time at the discretion of the investigator.
q. "Blank" predose urine sample to be collected within 24h prior to dosing *and* at intervals of 0-12h, 12-24h post oral dose, and at each subsequent 24h interval up to discharge. Forced void into the collection container at the end of the collection period. (see also Section 8.5.2).
r. "Blank" fecal sample to be collected at baseline from at least 1 bowel movement during the 48h predose interval, which may be collected from home. The last collected fecal sample will be used as the pre-dose sample and all previous pre-dose samples will be destroyed. Fecal samples will also be collected at intervals of 0-24 h post oral dose, and at each subsequent 24h interval up to discharge. (see also Section 8.5.2).

Table 2. Schedule of Activity (Cohort 2-Oral unlabeled PF-07220060 and IV [^{14}C]-PF-07220060 administration)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screen[a]		Study Period																FU phone call	Early Termination/ Discontinuation
Days relative to Day 1	Day (-28 to -2)	Day -1	Day 1												Day 2		Day 3	Day 4	Day 5-14[b]	Day 29-36	
Hours Relative to Oral Dosing of Unlabeled PF-07220060	-	-	0	0.5	1	2	2.5	2.75	3	4	6	8	12	16	24	36	48	72	96-312	-	-
Hours Relative to Dosing of [^{14}C]-PF-07220060 (IV infusion start)						0	0.5	0.75	1	2	4	6	10	14	22	34	46	70	94-310		-
Informed consent	X																				
Review of eligibility criteria	X	X																			
Inpatient stay at CRU		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X[b]		X
Medical history	X	X																			
Demography[c]	X																				
Review drug, alcohol/tobacco use[d]	X	X																	X[e]	X	X
Review prior and concomitant medications	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Physical examination[f]	X	X																	X[e]		X
Supine 12-lead ECG (single)	X		X							X									X[e]		X
Supine vital signs (blood pressure and pulse rate)	X		X							X									X[e]		X
Contraception Check[g]	X	X																		X	X
Serious and non-serious adverse event monitoring	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X
Oral Unlabeled PF-07220060 administration[h]			X																		
IV infusion of [^{14}C]-PF-07220060						X[i]															
Taste assessment[j]			X[k]																		
Emesis collection for radioactivity measurement, if occurs[k]			X	→	→	→	→	→	→	→	→	→	→	→	X	→	X	X			
Blood Samples for																					
PK of PF-07220060 [LCMS][l]			X	X	X	X			X	X	X	X	X	X	X	X	X	X	X		X
PK of [^{14}C]PF-07220060[m]	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

Table 2. Schedule of Activity (Cohort 2-Oral unlabeled PF-07220060 and IV [^{14}C]-PF-07220060 administration)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screen[a]		Study Period																	FU phone call	Early Termination/ Discontinuation
Days relative to Day 1	Day (-28 to -2)	Day -1	Day 1												Day 2		Day 3	Day 4	Day 5-14[b]	Day 29-36	
Hours Relative to Oral Dosing of Unlabeled PF-07220060	-	-	0	0.5	1	2	2.5	2.75	3	4	6	8	12	16	24	36	48	72	96-312	-	-
Hours Relative to Dosing of [^{14}C]-PF-07220060 (IV infusion start)						0	0.5	0.75	1	2	4	6	10	14	22	34	46	70	94-310		-
Metabolite identification			X	X	X	X				X	X	X	X		X		X	X	X[b,n]		
Clinical laboratory after ≥4hour fast	X	X															X		X[e]		X
Serology: HBsAg, HBsAb, HBcAb, HCVAb, and HIV[o]	X																				
Research Sample for Pharmcogenomics[p]			X[p]																		
Urine samples for																					
Drug test[q]	X	X																			
Cotinine test[q]	X	X																			
Spot collection for urinalysis (and microscopy, if needed)	X	X													X				X[e]		X
Total ^{14}C radioactivity/Metabolite identification[r]		X				X	→	→	→	→	→	→	X	→	X	→	X	X	X		
Feces samples for																					
Total ^{14}C radioactivity/Metabolite identification[s]		X				X	→	→	→	→	→	→	→	→	X	→	X	X	X		

a. Screening will be performed within 28 days prior to the single oral dose of PF-07220060.
b. See Section 4.1 for details on Cohort 2 discharge criteria.
c. Demographics will include participant race, ethnicity, age, gender, height, and weight during the screening visit.
d. The review of drug, alcohol/tobacco use may include an alcohol breath test or urine alcohol test or blood alcohol test (at discretion of investigator), which will be performed at screening, on Day -1 and at discharge. These tests may be performed at any other time at the discretion of the investigator.
e. Procedures to be performed only on the day of discharge or Day 14. No ECG or vital signs will be collected on Day 14. (see also Section 4.1).
f. Complete physical exam including height and weight will be performed by trained medical personnel at the CRU at screening or Day -1 only. A brief physical examination may be performed prior to discharge from the CRU and at other designated time points at the discretion of the investigator.

Table 2. Schedule of Activity (Cohort 2-Oral unlabeled PF-07220060 and IV [^{14}C]-PF-07220060 administration)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screen[a]		Study Period																	FU phone call	Early Termination/ Discontinuation
Days relative to Day 1	Day (-28 to -2)	Day -1	Day 1												Day 2		Day 3	Day 4	Day 5-14[b]	Day 29-36	
Hours Relative to Oral Dosing of Unlabeled PF-07220060	-	-	0	0.5	1	2	2.5	2.75	3	4	6	8	12	16	24	36	48	72	96-312	-	-
Hours Relative to Dosing of [^{14}C]-PF-07220060 (IV infusion start)						0	0.5	0.75	1	2	4	6	10	14	22	34	46	70	94-310		-

g. The investigator or his/her designee will discuss with the participant the need to use highly effective contraception consistently and correctly according to contraception guidelines.
h. PF-07220060 will be administered orally after overnight fasting of at least 10 hours on Day 1.
i. IV [^{14}C]PF-07220060 dose to be administered as an infusion over approximately 30 minutes (starting at approximately 2 hour after the administration of the oral unlabeled PF-07220060 dose).
j. Questionnaire to be completed by participants as soon as practically possible (within 1 min) after completion of dosing, *plus* at 5 min, 10 min, and 20 min post dose. PK samples will take the priority if the 2 procedures start to conflict.
k. Vomitus samples will be collected as described in Section 8.5.3.
l. Blood samples (approximately 4 mL) will be collected at pre dose (within approximately 1 hour prior to PF-07220060 dosing) and at post-dose time points indicated in the table up to discharge. If ECG and blood pressure/pulse rate assessments are scheduled at the same nominal time point as a PK sample, PK samples should be collected after completion of these assessments, with blood sampling for PK as close as possible to the planned timepoint. Blood samples will be processed to plasma as per instructions of the lab manual. (See also Section 8.5.1).
m. A 8 mL screening sample collection will be used to assess [^{14}C]PF-07220060 for screening only and will be stored for potential use as the diluent for post-dose AMS samples. Blood samples (approximately 4 mL) will be collected at preinfusion (within approximately 15 min prior to [^{14}C]PF-07220060 infusion) and at post-infusion time points indicated in the table up to discharge. If ECG and blood pressure/pulse rate assessments are scheduled at the same nominal time point as a PK sample, PK samples should be collected after completion of these assessments, with blood sampling for PK as close as possible to the planned timepoint. Blood samples will be processed to plasma as per instructions of the lab manual. (See also Section 8.5.1).
n. Cohort 2 blood samples (approximately 10 mL) for contigent use will be collected at predose (within approximately 1 hour prior to PF-07220060 dosing) and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 144 (if still in CRU) hours post-dose. If ECG and blood pressure/pulse rate assessments are scheduled at the same nominal time point as these samples, these samples should be collected after completion of these assessments with blood sampling for PK as close as possible to the planned timepoint. Blood samples will be processed to plasma as per instructions of the lab manual. (See also Section 8.5.1).
o. HBsAb will be tested if HBsAg and/or HBcAb are positive.
p. 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.
q. Urine drug and urine cotinine (mandatory) and alcohol breath test (at discretion of investigator) will be performed at screening, on Day -1. These tests may be performed at any other time at the discretion of the investigator.

Table 2. Schedule of Activity (Cohort 2-Oral unlabeled PF-07220060 and IV [^{14}C]-PF-07220060 administration)

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screen[a]		Study Period																	FU phone call	Early Termination/ Discontinuation
Days relative to Day 1	Day (-28 to -2)	Day -1	Day 1												Day 2		Day 3	Day 4	Day 5-14[b]	Day 29-36	
Hours Relative to Oral Dosing of Unlabeled PF-07220060	-	-	0	0.5	1	2	2.5	2.75	3	4	6	8	12	16	24	36	48	72	96-312	-	-
Hours Relative to Dosing of [^{14}C]-PF-07220060 (IV infusion start)						0	0.5	0.75	1	2	4	6	10	14	22	34	46	70	94-310		-

r. "Blank" predose urine sample to be collected within 24h prior to dosing ***and*** at intervals of 2-12h, 12-24h post oral dose, and at each subsequent 24h interval up to discharge. Forced void into the collection container at the end of the collection period. (see also Section 8.5.2).

s. "Blank" fecal sample to be collected at baseline from at least 1 bowel movement during the 48h predose interval, which may be collected from home. The last collected fecal sample will be used as the pre-dose sample and all previous pre-dose samples will be destroyed. Fecal samples will also be collected at intervals of 2-24 h post oral dose, and at each subsequent 24h interval up to discharge. (see also Section 8.5.2).

2. INTRODUCTION

PF-07220060 is a selective CDK4 inhibitor that is currently being investigated in Phase 1 studies (C4391001 and C4391002) in participants with metastatic or advanced solid tumors.

2.1. Study Rationale

The purpose of the study will be to investigate the metabolism and excretion following a single oral administration of [^{14}C]-PF-07220060 under fasted condition in healthy male participants. The data generated from this study will be used to assess the clearance mechanisms for PF-07220060 as well as identify metabolites that should be qualified to adhere to the ICH (M3) R2 guidance. In addition, this study will characterize the fraction of dose absorbed and bioavailability of orally administered PF-07220060 under the fasted condition, in reference to an IV infusion of [^{14}C]PF-07220060 (given as a microtracer microdose infusion following administration of an oral unlabelled dose), and will also assess PK parameters of PF-07220060 following both oral and IV administration of [^{14}C]PF-07220060.

This study will also evaluate sensory and taste attributes (eg, bitterness and tongue/mouth sensation) of the PF-07220060 oral suspension to guide the development of pediatric-friendly formulations.

2.2. Background

PF-07220060 is a selective CDK4 inhibitor that is currently being investigated in participants with metastatic or advanced solid tumors. PF-07220060 differs from currently approved dual CDK4/6 inhibitors in that it displays greater CDK4-over-CDK6 selectivity and is therefore hypothesized to drive tumor growth inhibition through greater CDK4 selectivity, while minimizing CDK6 driven hematopoietic effects. This may translate to improved efficacy and tolerability over other CDK4/6 inhibitors. The nonclinical PK/toxicokinetic, ADME properties of PF-07220060 have been evaluated in vitro and in vivo to support nonclinical safety evaluations and to assess the potential relevance to humans. The oral PK of PF-07220060 in nonclinical species indicated CCI oral bioavailability. The CCI metabolic pathways of PF-0720060 in vitro and in vivo included glucuronidation mediated by UGT2B7 and oxidation mediated by CYP3A4. Metabolites were found consistent between human in vitro system and other evaluated toxicology species (both in vitro and in vivo matrices). Renal excretion of PF-07220060 was CCI in rats and dogs.

The current study will investigate the absorption, metabolism and excretion of [^{14}C]-PF-07220060 as well as the absolute bioavailability and fraction absorbed of PF-07220060 using microtracer approach in healthy male participants.

2.2.1. Nonclinical Pharmacology

Details of the nonclinical pharmacology of PF-07220060 can be found in the current IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Following IV dosing in mouse, rat, and dog, PF-07220060 demonstrated CCI to CCI plasma CL (CCI%-CCI% of hepatic blood flow), CCI V_{ss} (CCI to CCI L/kg), and $t_{½}$ values ranging from CCI to CCI hours. Single-dose PK studies with PF-07220060 in these species indicated PF-07220060 had CCI oral bioavailability (%F in the range of CCI-CCI%). In 1-month toxicity studies, systemic exposure (C_{max} and AUC_{24}) of PF-07220060 CCI CCI and CCI was observed in rats and dogs. PF-07220060 had CCI plasma protein binding (fu ranging from CCI-CCI, CCI in human plasma) and there was CCI of PF-07220060 into CCI CCI in all evaluated species (mouse, rat, dog, and human).

In vitro and in vivo (after oral administration), the CCI metabolic pathways of PF-07220060 were glucuronidation and oxidation. The metabolite profile observed in human hepatocytes was CCI that in mouse, rat, and monkey hepatocytes; there were CCI that were CCI human. The CCI metabolism pathways observed in human hepatocytes CCI in the plasma of the rat and dog toxicology species. In vitro studies indicated the metabolism of PF-07220060 was CCI UGT-mediated (CCI%) with the CCI metabolism via CYP3A4 CCI%); in addition, UGT2B7 was the CCI enzyme involved in the formation of the CCI PF-07220060 glucuronide metabolite. Renal excretion of PF-07220060 was CCI in rats and dogs. In vitro studies indicate PF-07220060 to be a substrate of CCI and CCI

PF-07220060 has the potential for CCI of CCI in the gut and liver and to CCI at the relevant clinical exposures of CCI and 300 mg BID. PF-07220060 also has the potential for CCI CCI of CCI in the gut and liver at the relevant clinical exposures of 300 mg BID. Treatment with PF-07220060 CCI induced CCI in cryopreserved human hepatocytes. Treatment with PF-07220060 CCI or CCI at the CCI or CCI in human hepatocytes. Induction of CCI since it CCI It is thus CCI that PF-07220060 will CCI

Additional information on the nonclinical PK and metabolism of PF-07220060 is available in the current IB.

2.2.3. Nonclinical Safety

The toxicity profile of PF-07220060 was assessed in exploratory and 1-month pivotal GLP toxicity studies in rats and dogs. CCI respectively. The primary target organs identified were CCI

PF-07220060 was assessed in a series of genetic toxicity assays. All in vitro tests were conducted with and without exogenous metabolic activation using concentrations up to those limited by cytotoxicity, insolubility, or the acceptable limits of the test system. PF-07220060 was negative for mutagenicity in both the presence and absence of metabolic activation in the GLP microbial reverse mutation assays. Additionally, PF-07220060 was negative in the exploratory in vitro micronucleus assay in TK6 cells under all test conditions. In the GLP in vivo micronucleus assessment, PF-07220060 did not induce structural chromosome aberrations or polyploidy in nucleated cells from the bone marrow of male and female rats at CCI mg/kg/day, and was therefore, not considered clastogenic in that assay. However, PF-07220060 induced small but statistically significant increases in micronucleus formation in polychromatic erythrocytes from bone marrow in male rats ≥CCI mg/kg/day and in female rats at CCI mg/kg/day. PF-07220060 is non-mutagenic (negative in Ames) and non-clastogenic (negative in chromosome aberration), PF-07220060 poses no genotoxicity risk for single-dose lifetime experimentation in healthy Participants.

PF-07220060 had minimal activity in secondary pharmacology and ex vivo safety pharmacology assays, including weak activity (IC50 >CCI µM) toward the hERG channel. No cardiovascular effects (ECG or histopathology) were observed up to the highest dose tested (CCI mg/kg/day) in the pivotal dog study. In a conscious-telemetered dog GLP study, CCI mg/kg/day produced an CCI CCI only after the second dose; no effects were seen after the first dose. Relative to the C_{max} at the human dose of 100 mg, the NOEL for cardiovascular effect is CCIx.

In a GLP neuropulmonary safety study in rats, PF-07220060 administration did not result in any neurofunctional or pulmonary effects up to the highest dose tested. Relative to the C_{max} at the human dose of 100 mg, the NOEL for neuropulmonary safety is CCI×.

Additional information of the nonclinical safety of PF-07220060 is available in the current IB.

2.2.4. Clinical Overview

PF-07220600 is being evaluated as a single agent and in combination with ET in study C4391001 and in combination with PF-07104091 (a selective CDK2 inhibitor) in study C4391002. Included in this section are summaries of the interim results of the 2 ongoing studies.

Study C4391001 is a Phase 1/1b study of PF-07220060 in participants with advanced solid tumors with the purpose of evaluating safety, tolerability, PK, PD and anti-tumor activity of PF-07220060 as a single agent and in combination with ET. Study C4391002 is a Phase 1b/2 study of PF-07220060 and PF-07104091 in participants with mBC or other advanced solid tumors and in combination with ET (triplet combinations) in participants with metastatic/advanced mBC to evaluate the safety, tolerability, PK, PD, and antitumor activity of PF-07220060 and PF-07104091 combination.

2.2.4.1. Safety Overview

As of the data cut-off date of 02 September 2022 for C4391001, a total of 66 participants have been treated with PF-07220060; 34 participants have been treated with 100, 200, 300, 400, and 500 mg BID single agent PF-07220060. Thirteen participants have been treated with 300 mg BID, and 400 mg BID PF-07220060 in combination with letrozole. Thirteen participants have been treated with 300 mg BID and 400 mg BID PF-07220060 in combination with fulvestrant. Six participants have been treated with 400 mg BID single agent PF-07220060 with food. For the C4391001 study, the monotherapy MTD for PF-07220060 was determined to be 400 mg BID. The RDE for monotherapy was determined to be 300 mg BID.

As of 02 September 2022 for C4391001, 59 (89.4%) participants reported a total of 375 all-causality TEAEs. Twenty-three participants reported all-causality Grade 3 (22 [33.3%]) or 4 (1 [1.5%]) TEAEs and 1 (1.5%) participant experienced Grade 5 all-causality TEAEs. A total of 54 (81.8%) participants reported treatment-related TEAEs during the study. 16 (24.2%) of participants reported Grade 3 treatment-related TEAEs. No Grade 4 or 5 treatment-related TEAE were reported. A total of 4 (7.3%) participants of the 55 DLT evaluable participants experienced DLTs. A total of 13 (19.7%) participants reported all-causality SAEs; of these 3 (4.5%) participants reported SAEs which were considered to be related to the study drug by the investigator. A total of 3 (4.5%) participants discontinued the study due to AEs. One (1.5%) participant discontinued study due to AEs (leukopenia and neutropenia) in 300 mg BID + Letrozole cohort that were related to treatment drug, as per the investigator.

As of the data cut-off date of 12 September 2022 for C4391002, a total of 12 participants have received PF-07220060 in combination with PF-07104091 (selective CDK2 inhibitor) across 4 dose cohorts. Of the 12 treated participants, 10 (83.3%) participants reported a total of 88 TEAEs. Most frequently reported (≥20%) all-causality were nausea (58.3%), diarrhoea, neutrophil count decreased and white blood cell count decreased (50.0% each), anaemia (41.7%), lymphocyte count decreased (33.3%), fatigue, platelet count decreased and vomiting (25.0% each). No Grade 4 TEAEs were reported. One Grade 5 TEAE of disease progression was reported during the study. A total of 10 (83.3%) of the 12 participants reported treatment-related TEAEs. Most frequently reported (≥20%) treatment-related AEs were nausea (58.3%), diarrhoea, neutrophil count decreased and white blood cell count decreased (50.0% each), lymphocyte count decreased (33.3%), anaemia, fatigue, platelet count decreased and vomiting (25.0% each). No Grade 4 or 5 treatment-related TEAEs were reported during the study. As of the data cut-off date, there was 1 DLT (Grade 3 fatigue) reported in 1 participant who received PF-07220060 300 mg BID + PF-07104091 150 mg BID.

Further details on the clinical safety information with PF-07220060 are provided in the current IB.

2.2.4.2. Efficacy Overview

PF-07220060 has demonstrated early signs of anti-tumor activity in combination with ET in HR+/Her2- metastatic breast cancer patient population. Efficacy evaluation in dose expansion cohorts at RDE in combination with fulvestrant and letrozole is ongoing.

2.2.4.3. Summary of PF-07220060 Pharmacokinetics in Humans

In the ongoing study C4391001, as of 30 August 2022, preliminary PK data for PF-07220060 as monotherapy and in combination with ET was available from 60 participants with advanced solid tumors. PF-07220060 was administered orally as a single agent at doses ranging from 100 to 500 mg BID, and in combination with either letrozole or fulvestrant at 300 to 400 mg BID. Available plasma concentration-time data of PF-07220060 were analyzed using noncompartmental methods.

Preliminary PK results showed that PF-07220060 was rapidly absorbed following oral administration, with median T_{max} values of 1 to 4 hours. The plasma exposure parameters of PF-07220060, including C_{max}, AUC, and C_{min}, generally increased with dose from 100 to 300 mg BID for both Cycle 1 Day 1 and Cycle 1 Day 15. The steady state exposure was increased in a less than dose proportional manner. No substantial increase in plasma exposure was observed at doses higher than 300 mg BID. Moderate accumulation of the AUC was observed following repeated BID dosing. PK of PF-07220060 as monotherapy and in combination with letrozole or fulvestrant were generally comparable. PF-07220060 exhibited moderate inter-subject variability with geometric mean CV of 11-77% for steady state C_{max} and 40-70% for AUC_{tau} in the monotherapy cohorts, 24-42% for steady C_{max} and 15-28% for AUC_{tau} in the combination with ET cohorts.

Further details on the clinical PK of PF-07220060 are provided in the current IB.

2.3. Benefit/Risk Assessment

PF-07220060 will not provide any clinical benefit to healthy participants in this study. This study is designed primarily to assess human PK, absorption, metabolism, and elimination of PF-07220060 following oral and IV administrations. Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. Taking into account the measures to minimize risk to participants including single dose administration and close monitoring at CRU, the potential risks associated with PF-07220060 are justified by the anticipated benefits that may be afforded by furthering the understanding of PF-07220060.

Study C4391010 is the first time that [^{14}C]PF-07220060 will be administered to healthy adult participants, and will be the first time that IV infusions of PF-07220060 are administered to humans. Prior to this study, PF-07220060 has been administered as monotherapy or in combination with other anti-cancer agents to patients with advanced cancer at starting doses ranging from 100 mg to 500 mg BID continuously. Based on the available data from Study C4391001, the clinical safety profile favors further development of PF-07220060. Based on the results of the nonclinical toxicity studies (Section 2.2.3), the potential risk of PF-07220060 administration to healthy participants can be managed adequately, and be

mitigated with preventive measures in place that includes routine monitoring of AEs and changes in clinical laboratory test parameters for clinical management.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07220060 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: PF-07220060		
Potential effects of PF-07220060 on fertility, pregnancy, and lactation.	At this time, it is not known whether PF-07220060 can cause fetal harm when administered to pregnant women. Animal reproductive studies have not been conducted with PF-07220060. It is also not known whether PF-07220060 can affect male or female fertility, or whether PF-07220060 is secreted in human milk. PF-07220060 CCI CCI in rats and dogs on repeat administration and therefore, may potentially impact CCI	Eligibility criteria and the contraceptive lifestyle requirements (duration of caution of contraception CCI days for CCI participants) for this protocol have been crafted to mitigate these identified potential risks. Participants will be instructed and monitored on the contraceptive requirements implemented to minimize potential risks.
Potential risks associated with PF-07220060 include the following: hematological toxicities (including anemia and neutropenia) and gastrointestinal toxicities (such as nausea, vomiting and diarrhea).	The risks are based on emerging clinical data from the ongoing clinical study C4391001 following continuous administration of PF-07220060 to advanced cancer patients at doses ranging from 100 to 500 mg BID.	The present study will only test single 100 mg oral dose of PF-07220060 AEs and clinical laboratory results will be monitored on an ongoing basis.
Study Procedures		
Exposure to radiation	This study involves using radioactive markers (labels) during oral administration in Cohort 1 and IV infusion in Cohort 2. Radiation may cause side effects including fatigue, hair loss, nausea, vomiting, low blood counts, skin problems and even cancer.	The amount of radiation administered to each participant is very low, CCI nCi, either p.o. or i.v., and below the limit suggested in the FDA Guidance that could be exempted from dosimetry calculations. Based on long-standing experience, the radiation burden will be below 0.1 mSv, ie, ICRP Category I, trivial risk of health damage due to the exposure to ionising radiation.

2.3.2. Benefit Assessment

PF-07220060 will not provide any clinical benefit to healthy participants in this study. This study is designed primarily to further the understanding of human PK, absorption, metabolism, and elimination of PF-07220060 following oral and IV administrations.

2.3.3. Overall Benefit/Risk Conclusion

Based on available clinical data with PF-07220060 (Section 2.2.4 and current IB), a single 100 mg oral dose (Cohort 1), and a single 100 mg oral dose followed by CCI µg IV dose (Cohort 2) are anticipated to be safe and well tolerated. Each participant will be exposed to approximately CCI nCi over the entire study duration, which includes dosing [^{14}C]PF-07220060 in Cohort 1 and Cohort 2. This is classed as a microtracer dose, without any anticipated risk to study participants.

Based on the profile of PF-07220060 observed in nonclinical and clinical studies to date, and the measures taken as part of the study to minimize risk to study participants, the potential risks associated with PF-07220060 are justified by the anticipated benefits that may be afforded by furthering the understanding of PF-07220060.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the rate and extent of excretion of total radioactivity following administration of a single oral dose of [^{14}C]PF-07220060.	• Mass Balance: Cumulative recovery (%) of radioactivity in urine and feces (adjusted for vomitus, if any), expressed as a percent of total oral radioactive dose administered (quantification by AMS).
• To characterize the metabolic profile for PF-07220060 and identify the circulating and excreted metabolites of PF-07220060 following administration of a single oral dose of [^{14}C]PF-07220060.	• Metabolic profiling/metabolite identification and determination of relative abundance of [^{14}C]PF-07220060 and its metabolites in plasma, urine and feces, if possible (Cohort 1).
Secondary:	**Secondary:**
• To determine the absolute oral bioavailability (F) of PF-07220060 from a single oral dose of PF-07220060 under fasted conditions followed by a single IV microdose of [^{14}C]PF-07220060.	• The ratio of dose-normalized plasma AUC_{inf} of oral PF-07220060 (LCMS) and IV [^{14}C]PF-07220060 (HPLC-AMS) [Cohort 2 only].
• To determine the fraction of PF-07220060 dose absorbed (F_a) from a single oral dose of [^{14}C]PF-07220060 under fasted conditions.	• F_a calculated from the ratio of total recovered radioactivity [^{14}C] in urine following single dose administration of [^{14}C]PF-07220060 orally in Cohort 1 and via IV infusion in Cohort 2 (quantification by AMS).
• To determine the safety and tolerability of PF-07220060, administered as a single oral dose of [^{14}C]PF-07220060 or a single oral dose of PF-07220060 followed by administration of a single IV dose of [^{14}C]PF-07220060.	• AE monitoring, physical examination, clinical laboratory measurements, vital signs and 12-lead ECGs.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To characterize the metabolic profile and identify the circulating and excreted metabolites of PF-07220060 following administration of a single oral dose of PF-07220060 followed by administration of a single IV dose of [^{14}C]PF-07220060 (as needed).	• Contingent metabolic profiling/metabolite identification and determination of relative abundance of [^{14}C]PF-07220060 and the metabolites of [^{14}C]PF-07220060 in plasma, urine and feces, if possible (Cohort 2).
• To determine the plasma PK parameters of a single oral dose of PF-07220060 following administration as a single oral dose of [^{14}C]PF-07220060 or a single oral dose of PF-07220060 followed by administration of a single IV microdose of [^{14}C]PF-07220060.	• Plasma PK parameters of PF-07220060 from LCMS analyses (Cohort 1 and Cohort 2): • AUC_{last}, C_{max}, T_{max}. • If data permits: AUC_{inf}, $t_{½}$, V_z/F, CL/F.
• To determine plasma PK parameters of [^{14}C]PF-07220060 following administration	• Plasma PK parameters of [^{14}C]PF-07220060 from HPLC-AMS analyses (Cohort 2): • AUC_{last}, C_{max}, T_{max}.

Objectives	Endpoints
of a single IV microdose of [^{14}C]PF-07220060.	• If data permits: AUC_{inf}, $t_{½}$, CL, V_{ss}.
• To determine the urine PK parameters of PF-07220060 following administration as a single oral dose of [^{14}C]PF-07220060 (if measured)	• Urine PK parameters of PF-07220060 from LCMS (Cohort 1): • CL_R, Ae(∞), and Ae%.
• To determine plasma PK parameters of total radioactivity following administration of a single oral dose of [^{14}C]PF-07220060.	• Plasma PK parameters of total radioactivity [^{14}C] from AMS analyses (Cohort 1): • AUC_{last}, C_{max}, T_{max} of total radioactivity. • If data permit: AUC_{inf}, $t_{½}$.
• To determine plasma PK parameters of total radioactivity following a single oral dose of PF-07220060 followed by administration of a single IV dose of [^{14}C]PF-07220060 (as needed).	• Plasma PK parameters of total radioactivity [^{14}C] from AMS analyses (Cohort 2): • AUC_{last}, C_{max}, T_{max} of total radioactivity. • If data permit: AUC_{inf}, $t_{½}$.
• To explore the impact of pharmacogenomics on absorption, distribution, metabolism and excretion of [^{14}C]-PF-07220060 and the absolute bioavailability and fraction absorbed of PF-07220060.	• Allelic variants of drug metabolizing enzymes and transporters
• To evaluate the sensory and taste attributes of the PF-07220060 oral suspension in healthy participants under fasted conditions.	• Taste Assessment Survey Scoring Metrics: mouthfeel, bitterness, sweetness, sourness, saltiness, tongue/mouth burn, throat burn, and overall liking.

4. STUDY DESIGN

4.1. Overall Design

This study will be a Phase 1, open-label, parallel-group, single-dose study of PF-07220060 to characterize the metabolic profile and routes of excretion for oral [^{14}C]PF-07220060 and to evaluate F of PF-07220060 and F_a of [^{14}C]PF-07220060, in reference to IV mictrotracer [^{14}C]PF-07220060 in fasted healthy male participants.

In order to achieve sufficient bioanalytical sensitivity for the microtracer dose and differentiate the plasma concentrations resulting from the radiolabeled IV dose and those resulting from the oral dose, the ultra-sensitive AMS method will be used to quantify plasma concentrations of radiolabeled parent drug as well as total radioactivity [^{14}C] derived from the microtracer dose based on measurement of ^{14}C. Theoretically, F_a would be expected to be greater than F. In the event that F is estimated to be greater than F_a (because of the possibility that F is likely to be more precisely estimated due to analytical techniques), the greater of the

2 values will be used to represent the fraction of PF-07220060 absorbed. PF-07220060 will be considered highly permeable if either F or F_a is greater than 0.9 (as per BCS guidance).[2]

Approximately 6 healthy adult male participants will be enrolled in each of the 2 cohorts. Participants in Cohorts 1 and 2 will receive treatment regimen A and B, respectively. If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary and secondary PK objective(s), additional participants can be enrolled at the discretion of the investigator upon consultation with the sponsor. The SoA for Cohorts 1 and 2 (Table 1 and Table 2, respectively) describes procedures/assessments to be conducted from check-in to the CRU on Day -1 up to the discharge day occurring between Days 5 to 14 of each cohort.

Screening will occur within 28 days of the first dose of investigational product. All participants will provide informed consent and undergo screening evaluations to determine their eligibility. Eligible participants will be admitted to the CRU on Day -1. Prior to dosing in both Cohorts, pre-dose urine samples must be collected within 24 hrs prior to dosing and pre-dose fecal samples must be collected within 48 hrs prior to dosing (may be collected at home). The last collected fecal sample will be used as pre-dose sample and all previous pre-dose samples will be destroyed.

Regardless of whether or not the discharge criteria for each cohort have been met, no participant will be confined beyond Day 14 for both Cohorts. The maximum total in-house participation time for each participant in this study is approximately 15 days and 14 nights. Participants will have a follow-up phone call at 28-35 days after the last dose of study intervention.

Cohort 1: A single oral dose of 100 mg ^{14}C-labeled PF-07220060 containing approximately CCI nCi ^{14}C (ie, "lightly radiolabeled" or microtracer [^{14}C]PF-07220060) will be administered following an overnight fast of at least 10 hours. Dosing will involve administration of multiple rinses of the dosing container, and an assessment of the residual radioactivity on the dosing container will be required to be assessed and documented in the study CRF (see also Section 6.1.1). Blood, urine, feces, and vomitus (if any) samples will be collected as detailed in the SoA up until the discharge day occurs between Days 5 to 14. Discharge may occur for participants who meet at least one of the 2 radioactivity recovery criteria or reached the maximum duration of in-house stay. The discharge criteria are: (1) at least 90% of the administered radioactive dose has been recovered in urine+feces+vomitus (if any), (2) <1% of the administered radioactive dose has been recovered in urine+feces during 24-hour intervals over 2 consecutive days, or (3) the participant has reached Day 14. Each bowel movement must be collected, and time and date must be recorded. If an individual participant has not experienced a bowel movement within 36 hrs of their previous bowel movement, fluid intake should be increased and administration of a mild laxative (eg, prune juice or a mild stool softener) should be implemented, with the goal to facilitate at least once daily bowel movement. The use of the laxative should be recorded in the CRF.

Vomitus, if any, will be collected in full during the CCI hours after oral dosing in Cohort 1 and will be required to be prospectively tested for recovered radioactivity. For emesis that occurs

after [redacted] hours up to [redacted] hours post dose, samples will be collected in full and stored for potential reflex testing for recovered radioactivity. The time and date of any vomiting event within the first [redacted] hours post-dose must be recorded. Participants who experience emesis following oral dosing will not necessarily be excluded from analysis (see Section 9.3 for additional details on evaluable participants).

Cohort 2: A single oral dose of 100 mg unlabeled PF-07220060 will be administered following an overnight fast of at least 10 hours followed by an IV microtracer microdose of [redacted] µg [^{14}C]PF-07220060 containing approximately [redacted] nCi ^{14}C at the approximate time of anticipated peak plasma concentration (T_{max}). The ^{14}C IV dose will be administered as an infusion over approximately 30 minutes starting at approximately 2 hour (anticipated T_{max}) after the administration of the unlabeled oral dose. Blood, urine, feces, and vomitus (if any) samples will be collected as detailed in the SoA up until the discharge day occurs between Days 5 to 14. The duration of confinement for Cohort 2 will equal the longest individual participant duration of confinement in Cohort 1 so that the duration of urine sample collections over the periods is consistent to aid in accurate estimation of the F_a.

4.2. Scientific Rationale for Study Design

The purpose of the study is to assess the metabolism and excretion of [^{14}C]PF-07220060 following oral administration under fasted state conditions in healthy male participants. This information will enable assessment of primary and secondary clearance mechanisms of PF-07220060 as well as identify disproportionate metabolites that should be qualified to adhere to the ICH (M3) R2 guidance. In addition, this study will estimate the the fraction absorbed and bioavailability of oral PF-07220060 administered under fasted conditions in reference to an IV dose of [^{14}C]PF-07220060 and- will also assess plasma and urine PK parameters of PF-07220060 following both oral and IV administration of [^{14}C]PF-07220060. This characterization of absorption and oral bioavailability will enable the nomination of appropriate BCS designation for PF-07220060.

The study is being designed as a parallel-cohort study including 2 independent cohorts without crossover. Cohort 2 will be enrolled approximately 15 days after Cohort 1 enrollment. Cohorts 1 and 2 are enrolled sequentially using a single dose lifetime experimentation (one single PF-07220060 dose, no crossover) [redacted]

Only males will be included in this study given the desire to enroll a homogeneous population due to the small sample size of this study. Dosing of PF-07220060 is planned to occur in the fasted state, which is consistent with the administration condition in the dose finding and dose optimization parts of Phase 1 study C4391001 in patients with cancer.

Due to lack of data on the elimination half lives of PF-07220060 metabolites, the minimum duration of confinement of [redacted] days was set as the timeframe when circulating PF-07220060 is expected to reach BLQ levels as determined based on the plasma half-life estimate from population PK modeling. An additional [redacted] days of permitted extended stay is to allow for excretion of any unknown metabolites with longer half-lives.

The duration of confinement and collection of blood, urine, and fecal samples for the participants in Cohort 2 will be matched with as the longest one from Cohort 1 in order to best estimate the F_a of PF-07220060.

In this study, a "microtracer" approach will be used where the [^{14}C] dose is much lower than traditional ADME studies. With this approach, [^{14}C] will be quantified using an AMS detection technique. This technology allows ADME studies to be conducted without WBA data, as concentrations of [^{14}C] and resulting exposures are so minute that dosimetry calculations are not needed.[1]

Cohort 1 of the study is designed to evaluate the metabolic fate and mass balance of PF-07220060 following the intended clinical route of administration (oral) of [^{14}C]PF-07220060. In order to assess the metabolic fate of [^{14}C]PF-07220060, metabolites of [^{14}C]PF-07220060 circulating in plasma and eliminated in urine and feces following oral administration will be determined using AMS. Additionally, mass balance will be determined by recovery of total radioactivity excreted in urine and feces. Lastly, the plasma PK of PF-07220060 (via LCMS) will be compared to plasma PK of total radioactivity (via AMS) for determination of relative abundance as an additional way to quantify circulating metabolites.

Cohort 2 of the study is designed to evaluate the F and estimate F_a of the oral PF-07220060 dose. A microtracer microdose (CCI nCi, CCI µg) of [^{14}C]PF-07220060 will be administered via a 30 minutes IV infusion at the approximate T_{max} following an oral unlabeled 100mg- dose of PF-07220060 and labeled [^{14}C]PF-07220060 in plasma will be assessed via AMS following chromatographic separation (HPLC-AMS). F will be calculated as the ratio of dose-normalized plasma AUC_{inf} following orally administered PF-07220060 (ie, unlabeled PF-07220060 assessed by LCMS) to dose-normalized- plasma AUC_{inf} following intravenously administered [^{14}C]PF-07220060 (ie [^{14}C]PF-07220060 assessed by HPLC-AMS).

In **Cohort 2**, urine samples will also be collected at pre-specified intervals as described in the SoA and total radioactivity excreted in urine following intravenously administered [^{14}C]PF-07220060, will be measured via AMS. The ratio of dose-normalized total radioactivity recovered in urine following oral administration of [^{14}C]PF-07220060 in Cohort 1 to that recovered in urine following IV administration of [^{14}C]PF-07220060 in Cohort 2 will estimate the F_a following oral administration of [^{14}C]PF-07220060. Note, IV and oral radioactivities will be collected from participants in different cohorts. Also, this calculation of F_a assumes that metabolites generated during first pass are not renally eliminated and that parent drug excretion in urine is minimal for drugs that undergo first pass metabolism. Therefore, the computed F_a should be considered an approximation. There is no safety concern at time of discharge of Cohort 2 given that only a microtracer is dosed in this study.

Feces in Cohort 2 will be collected and will be assayed only after mass balance of [^{14}C]PF-07220060 from Cohort 1 and urinary radioactivity data from Cohort 2 is available and only if the study team determines that analysis of total radioactivity from feces of Cohort 2 would further inform disposition of PF-07220060 in humans.

To aid in the future development of a potential pediatric dosage form of PF-07220060, the current study will assess the taste attributes of the liquid formulation immediately after (within 1 mins) and over 20 mins post oral dose administration in both cohorts.

Banked biospecimens in both cohorts will be collected and stored for future exploratory analyses. Pharmacogenomic samples from both cohorts will be collected and analyzed for the purpose of assessing the impact of allelic variants of genes encoding metabolic enzymes such as CYP3A and UGT2B7 (the major metabolizing enzymes involved in the metabolism of PF-07220060 [Section 2.2.2]).

4.2.1. Choice of Contraception/Barrier Requirements

Studies to evaluate the developmental toxicity of PF-07220060 have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4 and Section 5.3).

4.3. Justification for Dose

In the Phase 1 study C4391001, PF-07220060 exhibited a CCI in steady state plasma exposures and CCI. 100 and 300 mg are the selected recommended doses for expansion cohorts and are currently being evaluated in a randomized fashion for dose optimization with the intention of one being selected as the dose for future Phase 3 trials. Both dose levels have been found to be safe and well tolerated in the Phase 1 study C4391001. For this study, a single dose level will provide the required data to adequately characterize the ADME profile of PF-07220060 and 100 mg was selected based on its greater exposure relative to dose size and likely higher oral bioavailability in comparison to CCI mg.

The anticipated plasma exposures of PF-07220060 following administration of a single 100 mg dose to male healthy volunteers in this study provide sufficient safety exposure margins (CCI x) over the exposures observed at NOAEL dose levels in the rat nonclinical safety study for single-dose lifetime experimentation in healthy participants (Section 2.2.3).

The radioactive dose administered in both cohorts would be approximately CCI nCi of ^{14}C. This dose of radioactivity will allow quantification of the [^{14}C]PF-07220060 by highly sensitive AMS analytical methodology (see Section 4.2 for details).

A microtracer microdose of CCI µg [^{14}C]PF-07220060 is planned in this study for IV administration in Cohort 2. The IV dose of CCI µg is CCI% (or approximately CCI) of the oral unlabeled dose of 100 mg and therefore expected to have negligible effect on the plasma PK of unlabeled PF-07220060. As per the ICH M3 (R2), human administration of an IV microdose of up to CCI µg can be supported with nonclinical toxicology studies where the drug is administered orally and without the need for additional nonclinical toxicology studies via IV route of administration.

4.4. End of Study Definition

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

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. 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 participants aged 18 to 65 years 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 their female partners (Section 10.4.2).

Other Inclusion Criteria:

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

3. Evidence of a personally signed and dated ICD indicating that the participant has been informed of all pertinent aspects of the study.

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

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, or HCVAb. Hepatitis B vaccination is allowed.

2. Participants with a history of irregular bowel movements (eg, regular episodes of diarrhea or constipation, IBS or lactose intolerance).

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 single oral dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

    - Concomitant use of any medications or substances that are strong inducers or inhibitors of CYP3A4 or UGT2B7 are prohibited within 5 half-lives plus 14 days (up to 28 days) prior to single oral dose of PF-07220060.

    - Use of proton-pump inhibitors is prohibited from 28 days prior to the first dosing of study intervention, and through the study. Other acid reducing agents including H2-receptor antagonists or local antacids should not be used for at least 7 days or 5 half-lives, whichever is longer, before the first dosing of study intervention and are prohibited within 5 days after the dosing.

5. Participants unwilling or unable to use a required concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

6. Previous administration with an investigational product (drug or vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives (whichever is longer) preceding the first dose of study intervention used in this study. Previous exposure to PF-07220060 or participation in studies requiring PF-07220060 administration.

7. Participants enrolled in a previous radionucleotide study or who have received radiotherapy within 12 months prior to screening or such that total radioactivity would exceed acceptable dosimetry.

Diagnostic Assessments:

8. A positive urine drug test. A single repeat for positive drug screen may be allowed.

9. 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 BP is ≥140 mm Hg (systolic) or 150 mm Hg (based on age) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

10. 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 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 is used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

11. Total ^{14}C radioactivity measured in plasma exceeding 11 mBq/mL.

12. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the studyspecific laboratory and confirmed by a single repeat test, if deemed necessary:

    - ALT, AST, bilirubin ≥1.05 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;

    - eGFR <60 mL/min/1.73 m^2 based on the 2021 CKD-EPI (combined serum creatinine plus serum cystatin C) equation;

    - Blood calcium or potassium <0.9 × LLN or >1.1 × ULN;

- Absolute neutrophil count <0.8 × LLN.

Other Exclusion Criteria:

13. 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) 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).

14. Use of tobacco or nicotine containing products within 3 months of screening or a positive urine cotinine test (ie, active smokers and those who currently use nicotine-containing products are excluded from participation in this study).

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

16. History of sensitivity to heparin or heparin-induced thrombocytopenia.

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

18. Participants whose occupation requires exposure to radiation or monitoring of radiation exposure.

19. 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 10.4.3) 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) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample on Day 1. No food will be allowed for at least 4 hours postdose on Day 1.
- On Day 1, water will be permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.
- Lunch will be provided approximately 4 hours after dosing on Day 1.
- Dinner will be provided approximately 9 to 10 hours after dosing on Day 1.
- An evening snack may be permitted.
- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.
- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.
- Participants will be asked to abstain from consuming indigestible materials (eg, corn, nuts, etc) for 2 days prior to dosing and for the duration of the study in order to facilitate ease of fecal homogenization.
- If an individual participant has not experienced a bowel movement in any 36 hour period post-dose, fluid intake should be increased and administration of a mild laxative (eg, prune juice or a mild stool softener) should be implemented.
- In Cohort 1, participants will be confined from the evening prior to the first dose until at least the morning of Day [redacted] hours postdose). If necessary, urine and/or fecal

collections will continue beyond Day [redacted] until Day 14 or until **one** of the following conditions are met:

- The amount of cumulative radioactivity recovered in excreta is at least 90% of administered radioactivity, **or**
- Less than 1% of the administered radioactivity has been recovered in excreta from 2 consecutive days (ie, total for urine + feces should <1% on 2 consecutive days).

The duration of confinement for Cohort 2 participants will equal the longest individual participants duration of confinement in Cohort 1.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to admission until discharge.
- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Participants will abstain from the use of tobacco- or nicotine-containing products for a period of 3 months before screening 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 96 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted;
- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing;

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

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

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational, 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-07220060 (either unlabeled or [^{14}C]PF-07220060).

6.1. Study Intervention(s) Administered

Study Intervention(s)			
Intervention Name	[^{14}C]PF-07220060	PF-07220060	[^{14}C]PF-07220060
Type	Drug	Drug	Drug
Use	Experimental	Experimental	Experimental
IMP or AxMP	IMP	IMP	IMP
Dose Formulation	Oral suspension	Oral suspension	IV solution
Unit Dose Strength(s)	100 mg	100 mg	CCI µg
Dosage Level(s)	100 mg, single dose	100 mg, single dose	CCI µg, single dose
Route of Administration	Oral	Oral	IV infusion
Sourcing	Provided centrally by the sponsor. Refer to EDR	Provided centrally by the sponsor. Refer to EDR	Provided centrally by the sponsor. Refer to TA.
Packaging and Labeling	[^{14}C]PF-07220060 components will be supplied by Pfizer as bulk API and bulk excipients for the extemporaneous preparation of the [^{14}C] labeled oral liquid formulation.	Unlabeled PF-07220060 and excipients will be supplied by Pfizer as bulk powders for extemporaneous preparation.	[^{14}C]PF-07220060 components will be supplied by Pfizer, as bulk API and, where necessary, bulk excipients for the manufacture of the [^{14}C] labeled IV liquid formulation at a GMP manufacturing facility.
SRSD	IB	IB	IB
Current/Former Name(s) or Alias(es)	NA	NA	NA

Study Arm(s)		
Arm Title	Cohort 1	Cohort 2
Arm Type	Experimental	Experimental
Arm Description	Oral dose of 100 mg PF-07220060 containing CCI nCi [^{14}C] ([^{14}C]PF-07220060) will be administered as an extemporaneously prepared liquid formulation.	Unlabeled oral dose of PF-07220060, 100 mg will be administered as an extemporaneously prepared liquid formulation. Approximately 2 hours after the administration of the unlabeled oral dose, a single dose of CCI µg PF-07220060 containing CCI nCi [^{14}C] ([^{14}C]PF-07220060) will be administered IV, as an infusion over approximately 30 minutes
Associated Intervention Labels	[^{14}C]PF-07220060	PF-07220060, [^{14}C]PF-07220060

For Cohort 1, [^{14}C]PF-07220060 investigational product for oral administration will be supplied by Pfizer as bulk API and, where necessary, bulk excipients for the extemporaneous preparation of an oral suspension at the clinic and will be presented to participants in individual dosing containers at the CRU.

For Cohort 2, unlabeled PF-07220060 investigational product for oral administration will be supplied by Pfizer as bulk API and, where necessary, bulk excipients for the extemporaneous preparation of an oral suspension at the clinic and will be presented to participants in individual dosing containers at the CRU.

In addition, [^{14}C]PF-07220060 investigational product will also be supplied by Pfizer as a bulk powder for preparation of an IV solution of [^{14}C]PF-07220060 at a GMP manufacturing facility.

The final product compositions and presentation will be detailed in a separate TA for the IV drug product and EDR for the oral drug products.

6.1.1. Administration

In Cohort 1, an oral dose of an extemporaneously prepared oral suspension of [^{14}C]PF-07220060 100 mg in 100 mL of 0.5% (w/v) methylcellulose in sterile water will be administered on Day 1.

In Cohort 2, an oral dose of an extemporaneously prepared oral suspension of unlabeled PF-07220060 100 mg in 100 mL of 0.5% (w/v) methylcellulose in sterile water will be administered approximately 2 hours before start of an IV infusion of [^{14}C]PF-07220060 CCI µg in CCI mL of 10 µg/mL PF-07220060 in CCI on Day 1.

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 on Day 1.

[^{14}C]PF-07220060 (100 mg dose; CCI nCi; Cohort 1): Following an overnight fast of at least 10 hours, participants will receive investigational product at approximately 0800 hours (plus or minus 2 hours). Dosing will involve administration of multiple rinses of the dosing container, and an assessment of the residual radioactivity on the dosing container will be required to be assessed and documented in the study CRF. Investigator site personnel will administer investigational product according to the EDR.

Unlabeled PF-07220060 (100 mg dose; Cohort 2): Following an overnight fast of at least 10 hours, participants will receive investigational product at approximately 0800 hours (plus or minus 2 hours). Investigator site personnel will administer investigational product according to the EDR.

[^{14}C]PF-07220060 (CCI µg dose; CCI nCi; Cohort 2): 10 mL of an IV solution of [^{14}C]PF-07220060 will be administered intravenously over 30 min as a continuous infusion through an infusion line starting 2 hours after administration of the oral dose. Administration of [^{14}C]PF-07220060 solution will be performed by qualified investigator site personnel (in accordance with local regulations and laws). Further details on administration will be outlined in the SAI.

In both cohorts, each participant will record the taste assessment at timed intervals of 0 MIN (ie, as soon as practically possible but within 1 minute post completion of dosing) as specified in the SAI, and at 5, 10, and 20 minutes after dosing using the sponsor provided Taste Assessment Questionnaire.

Administration of labeled and unlabeled PF-07220060 via oral and intravenous dosing routes will be performed by qualified investigator site personnel (in accordance with local regulations and laws). Please refer to the SAI for further details.

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 30 min 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 CRU local/site procedures.

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

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the CRU's local/site procedures. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider,

participant, in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

[^{14}C]PF-07220060 and unlabeled PF-07220060 oral suspension will be prepared in the CRU by 2 trained personnel. 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.

[^{14}C]PF-07220060 solution for the IV administration will be prepared at a GMP facility by 2 operators. Details of dose preparation will be given in a separate technical agreement. The prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site labeling requirements.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of Ips. Leftover containers following both oral and IV administration, including tubing used for infusion, should be retained for assessment of radioactivity if needed.

6.3. Assignment to Study Intervention

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator to allocate participants to cohorts and, in accordance with the randomization (allocation) numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization (allocation) number.

6.4. Blinding

This is an open-label study.

6.4.1. Blinding of the Sponsor

As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling, and/or supporting clinical development.

6.5. Study Intervention Compliance

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 CRU 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.

The site will complete the required dosage Preparation Record located in the EDR. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

6.6. Dose Modification

No dose modification is anticipated.

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-07220060 greater than CCI mg will be considered an overdose.

There is no specific treatment for a PF-07220060 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.**

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. 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.

As PF-07220060 is primarily metabolized by UGT2B7 and CYP3A4, as determined in in vitro studies, concomitant use of any medications or substances that are strong inducers and inhibitors of UGT2B7 and CYP3A4 are prohibited within 18 days (up to 28 days) and 28 days prior to dosing of study intervention respectively and within 4 days after the single oral dose of PF-07220060. Per in vitro studies, PF-07220060 is also indicated to be a CCI

CCI [redacted], thus, concomitant medications that are sensitive substrates for these enzymes should be used with caution.

Acid reducing agents may CCI [redacted] PF-07220060 absorption and systemic exposure. Use of CCI [redacted] is prohibited during the study and 28 days prior to dosing of study intervention. Other acid reducing agents including H2-receptor antagonists or local antacids should be washed out for at least 7 days or 5 half-lives, whichever is longer, before the dosing of study intervention and are prohibited within 5 days after the dosing.

All concomitant treatments taken during the study must be recorded with indication, daily dose, route of administration, 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

As this is a single dose study, it should be not applicable for this section.

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 Scys and 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.

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) **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 AND 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)	
Proteinuria	Confirmed proteinuria increase (1+ through 4+)	
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 new-onset or worsening albuminuria or proteinuria 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.

7.2. 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 procedures;

- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Investigator's decision.

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

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

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

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1 for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

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

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

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

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

The total blood sampling volume for individual participants in this study will be less than 500 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

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

8.2. Efficacy Assessments

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. BP should not be taken from the arm with an intravenous infusion. Participants should be instructed not to speak during measurements.

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

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

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

8.3.3. Electrocardiograms

Standard 12-lead ECGs 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.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

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

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocolrequired 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 48 hours 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 (see Section 7.1).

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

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

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

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

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

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

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

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE,

including a death, at any time after a participant has 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 nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

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

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications

and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A 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'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.

- 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 liveborn 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 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 completedreport 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 an incorrect study intervention;
- The administration of an incorrect dosage or incorrect combination of tablet dose strengths

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

8.5.1. Plasma for Pharmacokinetic Analysis of Total ^{14}C Radioactivity, PF-07220060, [^{14}C]-PF-07220060 and Metabolic Profiling

Blood samples of approximately 8 mL, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of total ^{14}C radioactivity by AMS and PF-07220060 by LCMS in Cohort 1 as specified in the SoA. The 8 mL screening blood sample will be used to assess ^{14}C total radioactivity for screening only and will be stored for potential use as the diluent for post-dose AMS samples. Blood samples of approximately 10 mL, will be collected into appropriately labeled tubes containing K_2EDTA for metabolite identification in Cohort 1 as specified in the SoA. Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL plasma, will be collected for measurement of PF-07220060 by LCMS in Cohort 2 as specified in the SoA. Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL plasma, will be collected for measurement of plasma concentrations of [^{14}C]PF-07220060 by AMS in Cohort 2 as specified in the SoA. A 8 mL screening sample collection will be used to assess [^{14}C]PF-07220060 for screening only and will be stored for potential use as the diluent for post-dose AMS samples. Blood samples of approximately 10 mL, will be collected into appropriately labeled tubes containing K_2EDTA for contingent use of metabolites identification in Cohort 2 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24 hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) 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 data collection tool (eg, 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 data collection tool (eg, CRF). If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor.

Samples will be used to evaluate the PK of total ^{14}C radioactivity, PF-07220060, [^{14}C]PF-07220060 and metabolic profiling. Samples collected for analyses of PF-07220060, total ^{14}C radioactivity, and ^{14}C PF-07220060 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 a bioanalytical method, or for other internal exploratory purposes.

The plasma PK samples collected for the measurement of [^{14}C]PF-07220060 (by HPLC-AMS) or Total ^{14}C radioactivity (by AMS) or PF-07220060 (by LCMS/MS) may be used for the measurement of Total ^{14}C radioactivity, [^{14}C]-PF-07220060 or metabolite profiling at Sponsor's discretion, as needed.

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

Samples collected for measurement of plasma concentrations of PF-07220060 will be analyzed using a validated analytical method in compliance with applicable SOPs. Total ^{14}C measurements, [^{14}C]PF-07220060 and metabolic profiling will be performed using a separate appropriate method based on AMS principles and methodology.

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

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

At the discretion of the Sponsor, one or more planned analyses may not be conducted if deemed unnecessary by the Sponsor based on emerging data.

8.5.2. Urine and Feces for Analysis of PF-07220060, Total ^{14}C Radioactivity and Metabolic Profiling

Urine will be collected for determination of PF-07220060, total ^{14}C radioactivity and metabolite profiling in Cohort 1, and will be collected for determination of total ^{14}C radioactivity and metabolite profiling (as needed) in Cohort 2, respectively as specified in the SoA. The participants in Cohort 1 and 2 will force void before oral dosing and before IV dosing, respectively. Prior to dosing on Day 1 (within 24 hours), each participant must empty his urinary bladder; an aliquot from this urine will serve as the "urine blank". The details regarding the collection, processing, storage and shipping of the urine samples will be provided in the lab manual.

Feces will also be collected for determination of total ^{14}C radioactivity and metabolite profiling in both periods as specified in the SoA. A pre-dose fecal sample is required within 48 hours prior to dosing [^{14}C]PF-07220060 in both cohorts. If multiple baseline fecal samples are collected for a participant, the one closest to dosing will be used as the baseline sample and all other fecal samples will be discarded.

Details of the collection of aliquots, volume, processing, storage and shipping of the urine and feces samples will be provided in the lab manual. The actual date and time (24-hour clock time) of each sample will be recorded.

For Cohort 1, samples collected for measurement of urine concentrations of PF-07220060 will be analyzed using a validated analytical method in compliance with applicable SOPs. Total ^{14}C measurements and metabolic profiling of urine samples will be performed using a separate appropriate method based on AMS principles and methodology. And total ^{14}C measurements and metabolic profiling of feces samples will be performed using a separate appropriate method based on AMS principles and methodology. For Cohort 2, analysis of metabolic profiling in urine and feces samples will be analyzed as needed for contingency as described by the lab manual.

Samples will be used to evaluate the recovery of total ^{14}C radioactivity, PF-07220060, [^{14}C]PF-07220060 and metabolic profiling. Samples collected for these analyses 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 a bioanalytical method, or for other internal exploratory purposes.

At the discretion of the Sponsor, one or more planned analyses may not be conducted if deemed unnecessary by the Sponsor based on emerging data.

8.5.3. Emesis (If any)

If emesis occurs within CCI hrs after dosing, then the vomitus must be collected in full and stored for a radioactivity assessment. For emesis that occurs after CCI hours up to CCI hours post dose, samples will be collected in full and stored for potential reflex testing of radioactivity recovered. All emesis including any swabbing, contaminated linens and facial tissues used to collect bodily discharge; eg, nose bleeding cleanup tissue and any emesis related cleanup is to be collected. The time and date of any vomiting event within the first CCI hours post-dose must be recorded.Participants who experience emesis following oral dosing will not necessarily be excluded from analysis (see Section 9.3 for additional details on evaluable participants).

8.5.4. Analysis of Dosing Solution and Determination of Administered Dose

In the IV cohort, the [^{14}C]-PF-07220060 dosing solution will be analyzed for total ^{14}C using LSC. Detailed storage and shipment procedures will be provided in the SAI and laboratory manual to the clinical site prior to the start of the clinical trial.

For oral administration of [^{14}C]-PF-07220060, the weight of [^{14}C]-PF-07220060 API powder weighed into each dosing bottle will be used in conjunction with the specific activity of the API to determine the exact dose administered. Residual radioactivity in the oral dosing container will be required to be assessed in Cohort 1 and documented in the study CRF.

For IV administration of [^{14}C]-PF-07220060, the dose volume administered will be controlled using pre-calibrated infusion pumps. The volume of IV dose (computed using weight of the dosing solution administered and the density of the dosing solutions), and concentration of PF-07220060 and radioactivity in dosing solution will be used to determine the exact dose administered for each participant.

The actual doses will be recorded in the CRF and will be used for PK analysis.

8.6. Genetics

8.6.1. Specified Genetics

A 4-mL blood PGx sample for DNA isolation will be collected into plastic K_2EDTA tubes, as defined in the SoA. The DNA sample will be analyzed for the purpose of assessing the impact of allelic variants of genes encoding drug metabolizing enzymes and transporters including, but not limited to, CYP3A and UGT2B7 on the ADME of the PF-07220060. Additionally, these samples may also be used for retrospective evaluation of additional genetic variants associated with variation in PK, biomarker response, or to explore AEs should these be observed. Samples will be retained for a period of up to 3 years after CSR finalization. In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in sponsor-identified study-specific central Laboratory Manual.

The PGx sample must be processed and shipped as indicated in the instructions provided to the investigator site, to maintain sample integrity. Any deviations from the PGx processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

8.6.2. Retained Research Samples for Genetics

Collection of retained research samples is not applicable to this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

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.

8.10. Taste Assessment

The sensory attributes of PF-07220060 will be evaluated by each participant using a Taste Assessment Questionnaire (Appendix 9) following oral dosing in both cohorts. Each participant will complete the Taste Assessment Survey immediately following dosing (within 1 min) *plus* at 5, 10, and 20 minutes post oral administration of [^{14}C]PF-07220060 or PF-07220060 oral suspension.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

There are no statistical hypotheses for this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Allocated to study intervention	"Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.
Mass balance analysis set	In Cohort 1, the mass balance population analysis set will be defined by evaluable participants who have received 1 dose of [^{14}C]PF-07220060 and who have completed total radioactivity concentration (urinary and fecal) data and who had no protocol deviations that may have affected the mass balance analysis. Further details what participants will be qualified as evaluable participants will be provided in the SAP, however, it should be noted that vomiting within CCI hours post oral dose or significant residual activity in the dosing container does not necessarily preclude participants from being evaluable.
PK Concentration	The PK concentration population for PF-07220060 is defined as all participants dosed with PF-07220060 (in both Cohort 1 and 2), who have at least one PF-07220060 concentration. The PK concentration population for [^{14}C] is defined as all participants dosed with [^{14}C]PF-07220060 (in both Cohort 1 and 2), who have at least one [^{14}C] measurement. The PK concentration population for [^{14}C]PF-07220060 is defined as all participants dosed with [^{14}C]PF-07220060 in

Participant Analysis Set	Description
	Cohort 2, who have at least one [^{14}C]PF-07220060 plasma concentration measurement.
PK Parameter	The PK parameter population for PF-07220060 is defined as all participants dosed with PF-07220060 (in both Cohort 1 or 2), who have at least one estimated PF-07220060 PK parameter of interest. The PK parameter population for total [^{14}C] is defined as all participants dosed with [^{14}C]PF-07220060 (in both Cohort 1 or 2), who have at least one total [^{14}C] PK parameters of interest. The PK parameter population for [^{14}C]PF-07220060 is defined as all participants dosed with [^{14}C]PF-07220060 in Cohort 2, who have at least one [^{14}C]PF-07220060 PK parameter of interest.
Safety	All participants allocated to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

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. Primary Endpoints

9.3.1.1. Mass Balance

Total Radioactivity in **urine** will be reported for **Cohort 1 and 2** separately, as the percentage of the administered radioactivity excreted at each time interval and as the cumulative total percent of dose excreted in urine over time.

Total Radioactivity in **feces** will be reported for **Cohort 1** (and if applicable for **Cohort 2**), as the percentage of the administered radioactivity excreted at each time interval and as the cumulativetotal percent of dose excreted in feces over time.

Total Radioactivity in **vomitus** (if any) will be reported for **Cohort 1 only**, as the percentage of the administered radioactivity excreted at each time interval and the total percent of dose recovered in vomitus.

Percent recovery of total radioactivity in urine, feces and vomitus for **Cohort 1 only**, will be determined based on total administered dose in **Cohort 1**. Residual radioactivity in the oral

dosing container will be required to be assessed in **Cohort 1** and documented in the study CRF.

Individual participant and median data profiles for total radioactivity will be graphically presented for the cumulative recovery of radioactivity in urine, feces and their combination over time in **Cohort 1 only**. Vomitus, if any, will be collected in full during the [CCI] hours after oral dosing in **Cohort 1** and will be required to be prospectively tested for recovered radioactivity. For emesis that occurs after [CCI] hours up to [CCI] hours post dose, samples will be collected in full and stored for potential reflex testing for recovered radioactivity. These participants will not necessarily be excluded from analysis. The total recovery of radioactivity in urine, feces (and vomitus, if any) and their combination will be listed and summarized for **Cohort 1 only**.

9.3.1.2. Metabolic Profiling and Metabolite Identification

Plasma, urine and fecal samples collected in Cohort 1 will be analyzed for metabolites of [^{14}C]PF-07220060. Major metabolites of PF-07220060 in plasma, urine and feces may be identified if possible. Contributions of parent and each major metabolite to total radioactivity recovered in urine and feces and to circulating radioactivity in plasma will be quantified if possible. Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the CSR.

9.3.2. Secondary Pharmacokinetic Endpoints

9.3.2.1. Absolute Oral Bioavailability

Absolute oral bioavailability (F) will be estimated as the ratio of geometric mean of dose-normalized AUC_{inf} for oral unlabeled and IV labeled PF-07220060 (from Cohort 2 only) as per the following equation:

$$F = [\text{PF-07220060\_}AUC_{po}/[^{14}C]\text{-PF-07220060\_}AUC_{iv}]*[[^{14}C]\text{-PF-07220060\_}Dose_{iv}/\ \text{PF-07220060\_}Dose_{po}]$$

Geometric Mean Ratio and 90% confidence interval: Natural log transformed AUC_{inf}(dn) (if data permit) and AUC_{last}(dn) from Cohort 2 will be analyzed using a mixed effect model with treatment as a fixed effect and participant variable as a random effect. Estimates of the adjusted (least squares) mean differences (Test/Reference) and the corresponding 90% confidence interval in log-scale will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric mean (Test/Reference) and 90% confidence interval for the ratio. IV [^{14}C]PF-07220060 will be considered the Reference formulation and unlabeled oral PF-07220060 will be considered the Test formulation.

9.3.2.2. Fraction Absorbed

Fraction of dose absorbed (F_a) will be estimated as the ratio of total radioactivity (dose normalized) excreted into the urine (from time 0 to the time of last measurable concentration)

following oral and IV administration of [^{14}C]PF-07220060 microtracer doses in Cohort 1 and 2, respectively:

$$F_a = [\%\ \text{Total}\ ^{14}\text{C\_Urine\_PO} / \%\ \text{Total}\ ^{14}\text{C\_Urine\_IV}]$$

Geometric Mean Ratio: The ratio (Test/Reference) of the geometric means of % Total ^{14}C in Urine will be estimated. Total ^{14}C_Urine_IV is the Reference and Total ^{14}C_Urine_PO is the Test.

A distribution-free method (nonparametric method, Hodges-Lehmann point estimate) may be conducted if extreme values are encountered in the PK parameters.

Cumulative urine ^{14}C amounts, percent ^{14}C dose as well as F_a (calculated using urine ^{14}C data, as described above) will be listed by treatment (Oral in Cohort 1 and IV in Cohort 2) and summarized using descriptive statistics. Individual and summary profiles of urine ^{14}C will be graphically presented.

In most circumstances, F_a estimation based on the urine method provides reliable F_a estimates. Total radioactivity following oral and IV administration will be generated from different people in separate cohorts, where physiological variability may lead to a less robust estimation of F_a. Different F_a calculation methods have been compared in detail and alternativeF_a calculation methods for this study may be investigated as needed based on emerging data.[3]

9.3.2.3. Safety Analyses

All safety analyses will be performed on the safety population.

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

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

9.3.3. Tertiary Pharmacokinetic Endpoints

9.3.3.1. Derivation of Pharmacokinetic Parameters

For **Cohort 1**, following a single oral administration of a microtracer dose of [^{14}C]PF-07220060, oral PK parameters for total [^{14}C] radioactivity will be derived from the concentration equivalent-time profiles, where appropriate. Additionally PK parameters for PF-07220060 will be computed based on LC/MS/MS analysis of plasma samples.

For **Cohort 2**, following a single oral dose of PF-07220060, PK parameters for PF-07220060 will be computed based on LC/MS/MS analysis of plasma samples.

For **Cohort 2**, following a single IV microtracer dose of [^{14}C]PF-07220060 at 2 hours post oral dose, IV plasma PK parameters of [^{14}C]PF-07220060 will be derived from plasma radioactivity concentration equivalent-time profiles following chromatographic separation of [^{14}C]PF-07220060 (ie. HPLC-AMS analysis).

The following plasma PK parameters will be derived (as data permits) from the concentration-time data using standard noncompartmental methods as outlined in Table 3 for the analytes and analysis methods listed in Section 3. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters. Actual administered [^{14}C] doses will be used for the total [^{14}C] and [^{14}C]PF-07220060 PK parameter calculations.

Table 3. Plasma PK Parameters Definitions

Parameter	Definition	Method of Determination
AUC_{last}[a]	Area under the plasma concentration-time profile from time 0 to time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal rule
AUC_{last}(dn)	Dose normalized AUC_{last} in Cohort 2 only	AUC_{last}/Dose
AUC_{inf}[a]	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 time point estimated from the log-linear regression analysis, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression
AUC_{inf}(dn)[a]	Dose normalized area under the plasma concentration-time profile from time 0 extrapolated to infinite time, in Cohort 2 only	AUC_{inf}/Dose
C_{max}	Maximum plasma concentration	Observed directly from data
C_{max}(dn)	Dose normalized maximum plasma concentration, in Cohort 2 only	C_{max}/Dose
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$
CL[a] (IV)	CL: systemic clearance	Dose/AUC_{inf}
V_{ss}[a] (IV)	V_{ss}: Steady state volume of distribution following IV infusion	CL × [MRT-(infusion time/2)] where MRT is the Mean Residence Time and is calculated as $AUMC_{inf}$/AUC_{inf} $AUMC_{inf}$ is the area under the first moment curve from 0 time to infinity.
CL/F[a] (oral)	Apparent clearance following oral administration	Dose/AUC_{inf}
Vz/F[a] (oral)	Apparent volume of distrubution following oral administration	Dose /(AUC_{inf}*k_{el})
F	Absolute oral bioavailability	[AUCpo/^{14}CAUCiv]*[[^{14}C]-PF-07220060_Doseiv/PF-07220060_Dosepo] where, AUCpo is PF-07220060 area-under-the-plasma concentration curve following oral administration of unlabelled PF-07220060 PF-07220060_Dosepo: Oral dose of unlabelled PF-07220060 ^{14}CAUCiv is PF-07220060 area-under-the-plasma concentration curve following IV administration of [^{14}C]PF-07220060 [^{14}C]-PF-07220060 Doseiv: IV dose of [^{14}C]-PF-07220060 AUC_{inf} will be used unless data do not allow estimation of AUC_{inf}, in which case, AUC_{last} will be used

a. If data permits.

The following urine PK parameters will be calculated using the outlied methods in Table 4.

Table 4 Urine PK Parameters Definitions

Parameter	Definition	Method of Determination
Total ^{14}C_Urine_PO	Total cumulative radioactivity excreted into urine from time 0 to the time of last measurable concentration following oral administration of [^{14}C]PF-07220060 (**Cohort 1** only)	Directly from observed [^{14}C] data
Total ^{14}C_Urine_IV	Total cumulative radioactivity excreted into urine from time 0 to the time of last measurable concentration following intravenously administered [^{14}C]PF-07220060 microtracer dose (**Cohort 2** only)	Directly from observed [^{14}C] data
% ^{14}C_Urine_PO	% of radioactivity in the urine following oral administration expressed as a percent of the radioactive dose administered (**Cohort 1** only)	(Total ^{14}C_Urine_PO/[^{14}C] $Dose_{po}$) *100 where, [^{14}C] $Dose_{po}$ is orally administered dose of [^{14}C]PF-07220060
% ^{14}C_Urine_IV	% of radioactivity in the urine following IV administration expressed as a percent of the radioactive dose administered (**Cohort 2** only)	(Total ^{14}C _Urine_IV/[^{14}C] $Dose_{iv}$) *100 where, [^{14}C] $Dose_{iv}$ is [^{14}C] intravenously administered dose of [^{14}C]PF-07220060
F_a	Fraction Absorbed	[Total ^{14}C_Urine_PO/Total ^{14}C_Urine_IV]*[^{14}Cdoseiv/^{14}Cdosepo]
Ae (PF-07220060 PO in Cohort 1)	Amount of unchanged drug excreted in urine	Sum of [PF-07220060 urine concentration* sample volume] for each collection interval
Ae% (PF-07220060 PO in Cohort 1)	Percent of dose recovered unchanged in urine	Ae/Dose*100
CLr (PF-07220060 PO in Cohort 1)	Renal clearance (oral)	Aet/AUCt where Aet is the amount of unchanged drug excreted in urine from 0 time until time t following oral dose of PF-07220060

9.3.3.2. Taste Assessment

The data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the questionnaire. The sensory attributes from the taste questionnaires (Appendix 9) will be listed and descriptively summarized by question across participants. Radar plots for each of the 4 time points, summarizing all attributes will be generated. Boxplots of each attribute will be plotted against the time points.

9.3.4. Other Analyses

Not applicable to this study.

9.4. Interim Analyses

No interim analysis will be conducted for this study.

9.5. Sample Size Determination

Approximately 6 healthy adult male participants will be enrolled in each of the 2 cohorts based on the industry standard sample size for mass balance and radiolabeled microtracer studies. This sample size was not chosen based on any empirical data or hypothesis testing criteria.

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.

10.1.4. 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 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

In certain situations, sponsor review of redacted copies of participant medical records for prior illegal drug, alcohol, and tobacco use, as well as blood donation within 60 days prior to first dose of PF-07220060 may be performed, 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

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 CTMS.

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, and (d) Pfizer Call Center number.

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. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 5. Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Reticulocyte count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine Cystatin C[a] eGFR[b] Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein For suspected DILI: AST/ALT T bili, albumin, CK, direct and indirect bili GGT, PT/INR, eosinophils (%), alkaline phospatase Acetaminophen/paracetamol Hepatitis serology (even if screening negative) For suspected DICI/DIKI: Creatinine (Screat) Cystatin C[a] (Scys) eGFR (Screat only and combined Screat+Scys) eCrCl[b]	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy[c]	Urine Drug Screening[d] Urine Cotinine At screening: • Hepatitis B surface antigen • Hepatitis B surface antibody[e] • Hepatitis B core antibody • Hepatitis C antibody • HIV

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 serum creatinine increase post-baseline is observed (see Section 7.1.1).
b. Screening and Baseline eGFR or eCrCl 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. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.

Table 5. Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other

d. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site- and study-specific).
e. HBsAb will be tested if HBsAg and /or HBcAb are positive.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

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

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

10.3.1. Definition of AE

AE Definition

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

Events 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:
  - Is associated with accompanying symptoms;
  - Requires additional diagnostic testing or medical/surgical intervention;
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE 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. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been 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. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

* **EDP** (with or without an associated 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 theiropinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

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

- 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 [redacted] days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) plus an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either:

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

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- The male participant should be advised of the benefit for a WOCBP partner using a highly effective method of contraception with a failure rate of <1% per year, as described in Section 10.4.3.

10.4.2. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female

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

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

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

10.4.3. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

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 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:
- Samples for specified genetic analysis (see Section 8.6.1) will be stored for up to 3 years or other period as per local requirements.
- 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. If on further evaluation the abnormal test result is repeated, the participant should be discontinued from the study and adequate, immediate, supportive measures taken.

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 [Screat-based eGFR] or creatinine clearance [eCrCl]). 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 Table in 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)[4]

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 (ie, eGFR or eCrCl) will be according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria for both pediatric and adult participants.

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 x 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	eGFR 30 to 59 mL/min/1.73m² OR	eGFR 15 to 29 mL/min/1.73m² OR	eGFR <15 mL/min/1.73m² OR eCrCl <15	Death

	eCrCl ≥60 to 80 mL/min	eCrCl 30 to 59 mL/min	eCrCl 15 to 29 mL/min	mL/min OR dialysis indicated	
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 PEDIATRICS: Urine Protein-to-Creatinine Ratio (UPCR) 0.5 to 1.9	ADULTS: Proteinuria 4+ OR Proteinuria ≥3.5 g/24 h PEDIATRICS: Urine Protein-to-Creatinine Ratio (UPCR) >1.9	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. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by >60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30-second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as SAEs

• QTcF prolongation >500 ms.
• Absolute value of QTcF > 450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• New-onset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

The 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: Oral Solution or Suspension Palatability Questionnaire

1. Questionnaire should be administered to adult participants, preferably by the clinician or the nurse.

2. Use **colored copy** of the Palatability Questionnaire.

3. **Do not alter (reduce or enlarge) the original size of the Palatability Questionnaire**.

4. Please collect the following background information:

Background Information

Study #/Study Site	
Period and Day	
Participant ID (Rand ID)	
Treatment	
Collect Date	
Questionnaire Fully Completed (circle one)	Yes/No

Please answer the following questions and provide a mark (✕) on the color bar at 1 (immediately), 5, 10 and 20 minutes after dosing. Please ensure participant has access to these descriptions when completing the questionnaire.

Q1: Bitterness – Please tell us about the degree of bitterness of the product you tasted.

Q2: Tongue/mouth burn – Please tell us about the degree of tongue/mouth burn of the product you tasted.

Q3: Throat burn – Please tell us about the degree of throat burn of the product you tasted.

Example: How to provide a mark (✕) on the color bar.

Within 1 minute (immediately) after dosing

Provide a mark (×) <u>on the color bar</u>.

Bitterness	Tongue/Mouth Burn	Throat Burn
Not Bitter	No Burn	No Burn
		
Extremely Bitter	Extreme Burn	Extreme Burn

5 minutes after dosing

Provide a mark (×) <u>on the color bar</u>.

Bitterness	Tongue/Mouth Burn	Throat Burn
Not Bitter	No Burn	No Burn
		
Extremely Bitter	Extreme Burn	Extreme Burn

10 minutes after dosing

Provide a mark (✕) <u>on the color bar</u>.

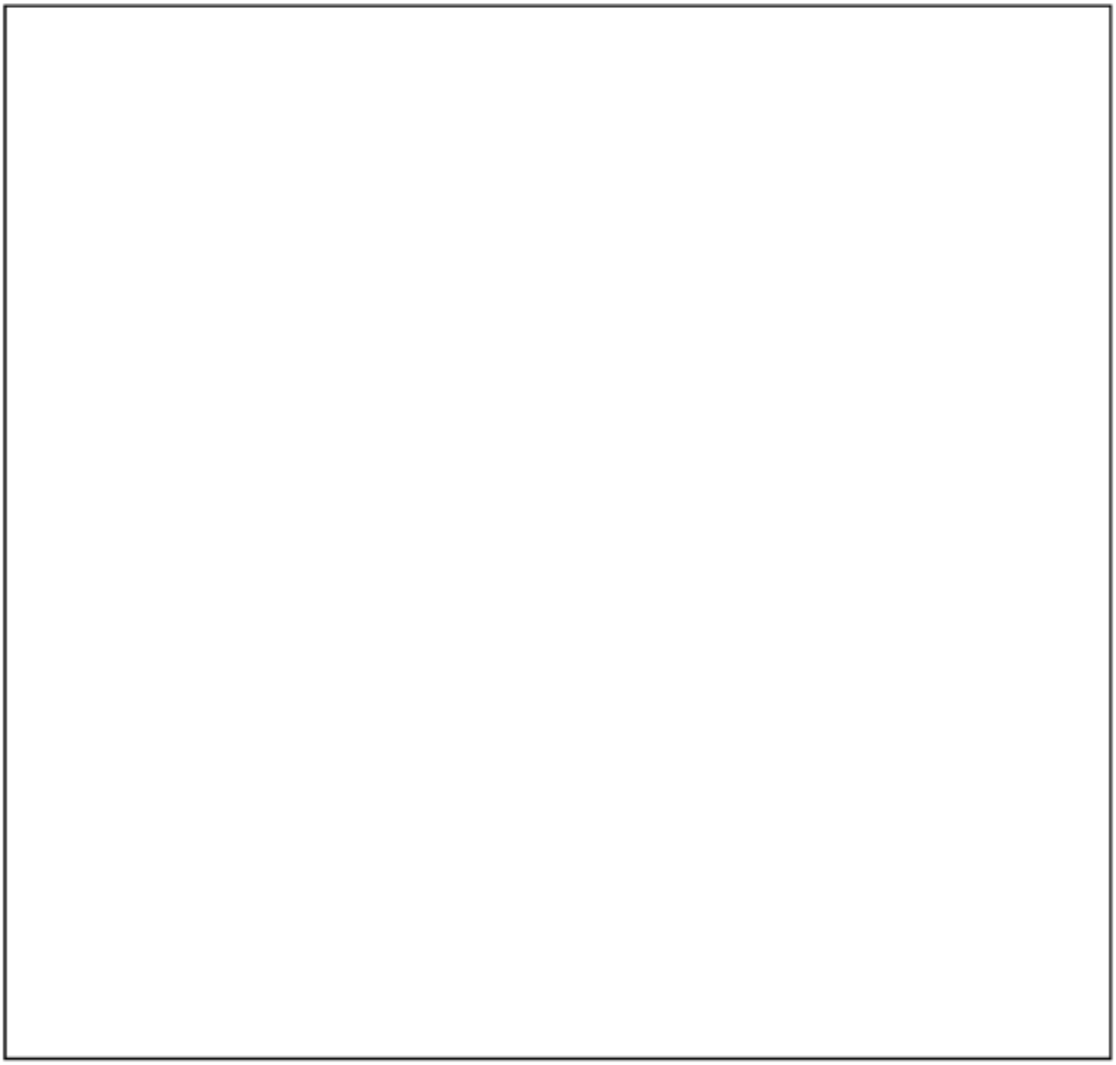
Bitterness	Tongue/Mouth Burn	Throat Burn
Not Bitter	No Burn	No Burn
		
Extremely Bitter	Extreme Burn	Extreme Burn

20 minutes after dosing

Provide a mark (✕) <u>on the color bar.</u>

Bitterness	Tongue/Mouth Burn	Throat Burn
Not Bitter	No Burn	No Burn
		
Extremely Bitter	Extreme Burn	Extreme Burn

Additional Feedback – After completing the "20 minute after dosing" palatability questions, please provide any additional descriptive feedback in the box below regarding the taste or odor of the product.



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
ADME	Absorption, Distribution, Metabolism and Excretion
AE	adverse event
Ae%	Percent of dose recovered unchanged in urine
Ae(∞)	Cumulative amount of unchanged drug excreted in urine from time 0 extrapolated to infinite time
AKI	acute kidney injury
ALT	alanine aminotransferase
AMS	accelerator mass spectrometry
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the plasma concentration-time profile from time 0 to 24 hours post dose
AUC_{inf}	area under the plasma concentration time profile from time 0 extrapolated to infinite time
AUC_{inf}(dn)	dose normalized AUC_{inf}
AUC_{last}	area under the plasma concentration-time profile from time 0 to time of the last quantifiable concentration
AUC_{last}(dn)	dose normalized AUC_{last}
AUC_{tau}	Area under the plasma concentration-time curve over the dosing interval
AV	atrioventricular
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
CCI	[redacted]
BCS	Biopharmaceutics Classification System
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology

Abbreviation	Term
CL	systemic clearance
CL/F	apparent clearance
CL_R	renal clearance
C_{max}	maximum observed concentration
C_{max}(dn)	dose normalized C_{max}
CMC	Chemistry, Manufacturing and Controls
C_{min}	the minimum blood plasma concentration reached by a drug during a dosing interval
CO_2	carbon dioxide (bicarbonate)
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
CTMS	Clinical Trial Management System
CV	coefficient of variation
CYP	cytochrome P450
DCT	data collection tool
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
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
eSAE	electronic serious adverse event
ET	endocrine therapy
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
F	oral bioavailability
F_a	fraction absorbed
FDA	Food and Drug Administration

Abbreviation	Term
FSH	follicle-stimulating hormone
FU	follow-up
fu	fraction unbound
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacture Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
Her2-	human epidermal growth factor receptor 2 negative
hERG	Human ether-à-go-go related gene
HIV	human immunodeficiency virus
CCI [redacted]	
HPLC	high performance liquid chromatography
HR	heart rate
HR+	hormone receptor positive
HRT	hormone replacement therapy
IB	Investigator's Brochure
IBS	irritable bowel syndrome
IC50	50% inhibitive concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRP	International Commission on Radiological Protection
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous(ly)
K	Proportionality constant for Schwartz Equations (kidney function)
KDIGO	Kidney Disease Improving Global Outcomes
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LBBB	left bundle branch block
LCMS	liquid chromatography mass spectrometry
LC/MS/MS	Liquid chromatography tandem mass spectrometry
LFT	liver function test
LLN	lower limit of normal
LSC	Liquid Scintillation Counting
CCI [redacted]	

Abbreviation	Term
mBC	Metastatic breast cancer
MCV	mean corpuscular volume
CCI	
MQI	medically qualified individual
MREC	Medical Research Ethics Committee
CCI	
MTD	maximum tolerated dose
NA	not applicable
NL	the Netherlands
NOAEL	no observed adverse effect level
NOEL	No observed effect level
CCI	
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
CCI	
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PO	oral(ly)
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RDE	Recommended dose for expansion
RFI	request for information
RNA	ribonucleic acid
SAE	serious adverse event
SAI	Site Administration Instructions
SAP	Statistical Analysis Plan
CCI	
SC	subcutaneous
SCL	supply chain lead
Screat	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
SRSD	Single Reference Safety Document

Abbreviation	Term
CCI [redacted]	
ST-T	ST segment and T wave
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Terminal phase elimination half-life
TA	Technical Agreement
TB	tuberculosis
T bili	total bilirubin
CCI [redacted]	
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TK6	thymidine kinase cells
T_{max}	time for C_{max}
UACR	urine albumin/creatinine ratio
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
US	United States
UTI	urinary tract infection
V_{ss}	steady state volume of distribution
V_z/F	apparent volume of distribution
WBA	whole body autoradiography
WBC	white blood cell
WOCBP	woman/women of childbearing potential

[redacted]

11. REFERENCES

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