A PHASE 1, OPEN-LABEL, 2-PERIOD, FIXED SEQUENCE STUDY TO INVESTIGATE THE ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION OF [^{14}C]PF-07081532 AND TO ASSESS THE ABSOLUTE BIOAVAILABILITY AND FRACTION ABSORBED OF PF-07081532 IN HEALTHY MALE PARTICIPANTS USING A [^{14}C]-MICROTRACER APPROACH

Study Intervention Number:	PF-07081532
Study Intervention Name:	NA
US IND Number:	CCI
EudraCT/CTIS Number:	NA
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	NA
Protocol Number:	C3991006
Phase:	1

Brief Title: Phase 1 Study in Healthy Male Participants to Assess ADME Properties of [^{14}C]PF-07081532

Document History

Document	Version Date
Original protocol	30 September 2022

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1, Open-Label, 2-Period, Fixed Sequence Study to Investigate the Absorption, Distribution, Metabolism and Excretion of [^{14}C]PF-07081532 and to Assess the Absolute Bioavailability and Fraction Absorbed of PF-07081532 in Healthy Male Participants Using a [^{14}C]-Microtracer Approach

Brief Title:

Phase 1 Study in Healthy Male Participants to Assess ADME Properties of [^{14}C]PF-07081532

Regulatory Agency Identification Number(s):

US IND Number:	CCI
EudraCT/CTIS Number:	NA
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	NA
Protocol Number:	C3991006
Phase:	1

Rationale:

The purpose of the study is to assess the metabolism and extent of excretion of [^{14}C]PF-07081532 in urine and feces, following oral administration, in the fed state, in healthy male participants. This information will enable assessment of clearance mechanisms of PF-07081532 as well as identify disproportionate metabolites that should be qualified to adhere to the ICH M3 (R2) MIST guidance. In addition, this study will characterize the fraction of dose absorbed and the bioavailability of orally administered PF-07081532 in the fed state, in reference to an IV dose of [^{14}C]PF-07081532, while it will also assess PK parameters following both oral and IV administration of [^{14}C]PF-07081532.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the extent of excretion of total radioactivity in urine and feces following administration of a single oral dose of [^{14}C]PF-07081532.	• Total recovery of radioactivity in urine and feces, and both routes combined, expressed as a percent of total oral radioactive dose administered.
• To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of [^{14}C]PF-07081532.	• Metabolic profiling/identification and determination of relative abundance of [^{14}C]PF-07081532 and the metabolites of [^{14}C]PF-07081532 in plasma, urine, and feces.
Secondary:	**Secondary:**

• To quantify plasma PK parameters of PF-07081532 and total radioactivity following administration of a single oral dose of [^{14}C]PF-07081532.	• AUC_{last}, C_{max}, T_{max}, and if data permit, AUC_{inf}, $t_{½}$, CL/F (PF-07081532 only), and Vz/F (PF-07081532 only), to describe single oral dose PK in Period 1 of:
	  • Total radioactivity in plasma;
	  • PF-07081532 in plasma.

• To quantify plasma PK parameters of [^{14}C]PF-07081532, following administration of a single, IV, microdose of [^{14}C]PF-07081532.	• [^{14}C]PF-07081532 parameters to describe IV plasma PK: AUC_{last}, AUC_{last}(dn), C_{max}, C_{max}(dn), T_{max}, and if data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, CL, V_{ss} and MRT.
• To determine the absolute oral bioavailability (F) of PF-07081532 following administration of a single oral dose of PF-07081532 compared to a single IV microdose of [^{14}C]PF-07081532.	• F computed from plasma AUC_{inf} (if data permit, otherwise AUC_{last}) of oral unlabeled PF-07081532 in Period 2 and IV microdose of [^{14}C]PF-07081532 in Period 2.
• To determine the fraction of dose absorbed (F_a) following administration of a single oral dose of [^{14}C]PF-07081532.	• F_a calculated from ratio of total urinary radioactivity following oral administration of [^{14}C]PF-07081532 in Period 1 and IV administration of [^{14}C]PF-07081532 in Period 2.
• To evaluate safety and tolerability of PF-07081532, administered as a single oral dose of [^{14}C]PF-07081532 or a single oral dose of PF-07081532 followed by administration of a single IV microdose of [^{14}C]PF-07081532.	• Safety endpoints including physical examinations, adverse events, clinical laboratory measurements, vital signs, and ECG.

Overall Design:

This study is a Phase 1, open-label, 2-period, fixed sequence study to characterize the metabolic profile and routes of excretion of oral [^{14}C]PF-07081532 and to evaluate the absolute oral bioavailability (F) and fraction absorbed (F_a) of PF-07081532 in healthy male participants.

Number of Participants:

Approximately 6 participants will be enrolled in the study.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to and dosing with study intervention. 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:

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

1. Male participants must be 18 to 60 years of age, inclusive, at the time of signing the ICD.

2. Male participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, blood pressure and pulse rate measurement, standard 12-lead ECG, and laboratory tests.

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

4. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures including collection of blank urine and feces samples prior to dosing on Day 1, Period 1.

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

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).

    - Positive testing at screening for HIV, HBsAg, HBcAb, HBsAb or HCVAb. Note: A positive HBsAb due to hepatitis B vaccination is permissible.

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

3. History of irregular bowel movements (eg, irritable bowel syndrome, frequent episodes of diarrhea, or constipation defined by less than 1 bowel movement on average per 2 days) or lactose intolerance.

4. Other medical or psychiatric condition including recent (within the past year of screening) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg, contact with positive case) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

5. Use of any prescription or non-prescription drugs and dietary and herbal supplements.

6. Previous administration with an investigational product (drug or vaccine) within 90 days (or as determined by the local requirement) preceding the first dose of study intervention used in this study.

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

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

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

10. eGFR <90 mL/min/1.73m^2 (calculated with the 2021 CKD-EPI Scr only equation) at screening.

11. 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 the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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

    - AST **or** ALT level ≥1.5 × ULN;

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

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

15. History of sensitivity to heparin or heparin-induced thrombocytopenia ***only if*** heparin is planned to flush IV catheters.

16. Total [^{14}C] radioactivity measured in plasma at screening exceeding 11 mBq/mL.

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

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-07081532	PF-07081532	[^{14}C]PF-07081532
Arm Name (group of participants receiving a specific treatment or no treatment)	Period 1	Period 2	Period 2
Type	Drug	Drug	Drug
Dose Formulation	Extemporaneously prepared liquid formulation	Extemporaneously prepared liquid formulation	Extemporaneously prepared liquid formulation
Unit Dose Strength(s)	NA	NA	NA
Dosage Level(s)	30 mg, single dose	30 mg, single dose	100 µg, single dose
Route(s) of Administration	Oral	Oral	IV infusion
Use	Experimental	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the SAI	Provided centrally by the sponsor. Refer to the SAI	Provided centrally by the sponsor. Refer to the SAI
Packaging and Labeling	[^{14}C]PF-07081532 components will be supplied by Pfizer, as bulk API and, where necessary, bulk excipients for the manufacture of the [^{14}C] labeled oral liquid formulation	Unlabeled PF-07081532 will be provided by Pfizer as bulk powders for extemporaneous preparation	[^{14}C]PF-07081532 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
Current/Former Name(s) or Alias(es)	[^{14}C]PF-07081532	PF-07081532	[^{14}C]PF-07081532

Study Arm(s)		
Arm Title	Period 1	Period 2
Arm Type	Experimental	Experimental
Arm Description	Oral dose of 30 mg PF-07081532 containing 250 nCi [^{14}C] ([^{14}C]PF-07081532) will be administered as an extemporaneously prepared liquid formulation, approximately 10 minutes after completion of breakfast.	Unlabeled oral dose of PF-07081532, 30 mg will be administered as an extemporaneously prepared liquid formulation, approximately 10 minutes after completion of breakfast. Approximately 1 hour after the administration of the unlabeled oral dose, a single dose of 100 µg PF-07081532 containing 250 nCi [^{14}C] ([^{14}C]PF-07081532) will be administered IV, as an infusion over approximately 15 minutes.
Associated Intervention Labels	[^{14}C]PF-07081532	PF-07081532, [^{14}C]PF-07081532

Statistical Methods:

A sample size of approximately 6 participants has been chosen based on the industry standard sample size for mass balance and radiolabeled microtracer studies and in line with latest FDA draft guidance (May 2022). This sample size was not chosen based on any empirical data or hypothesis testing criteria. The sample size has been selected to ensure that 6 participants provide evaluable data after completing Period 1; with intent to replace participants who prematurely withdraw (or offer non-evaluable or partially evaluable data). In Period 2, participants who are prematurely withdrawn may be replaced at the discretion of sponsor.

Extent of excretion (**Period 1 only**): Radioactivity excreted in urine and/or feces will be reported as the percentage of the administered radioactivity excreted at each time interval, cumulatively through that interval and the total percent of dose recovered in urine and/or feces. Percent recovery and cumulative recovery of total radioactivity in urine, feces and emesis (if any) will be determined based on total administered dose.

Metabolic Profiling and Metabolite Identification (**Period 1 only**): Major metabolites of PF-07081532 in plasma, urine, and feces following oral dose of [^{14}C]PF-07081532 will 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. Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the CSR.

Absolute bioavailability (**Period 2 only**): F will be estimated as the ratio of adjusted geometric means of dose-normalized AUC_{inf} (if data permit, otherwise AUC_{last}) for oral unlabeled PF-07081532 and IV [^{14}C]PF-07081532 in plasma.

Fraction absorbed (F_a): F_a will be estimated as the ratio of adjusted geometric means of % of administered radioactive dose excreted into urine following oral and IV administration of [^{14}C]PF-07081532 in **Periods 1 and 2**, respectively. Urine radioactivity up to Day 7 will be used for Period 1 to match the duration of Period 2 urine collection up to discharge.

PK parameters (**Period 1**): Plasma PK parameters of PF-07081532 and total radioactivity will be calculated following administration of a single oral dose of [^{14}C]PF-07081532.

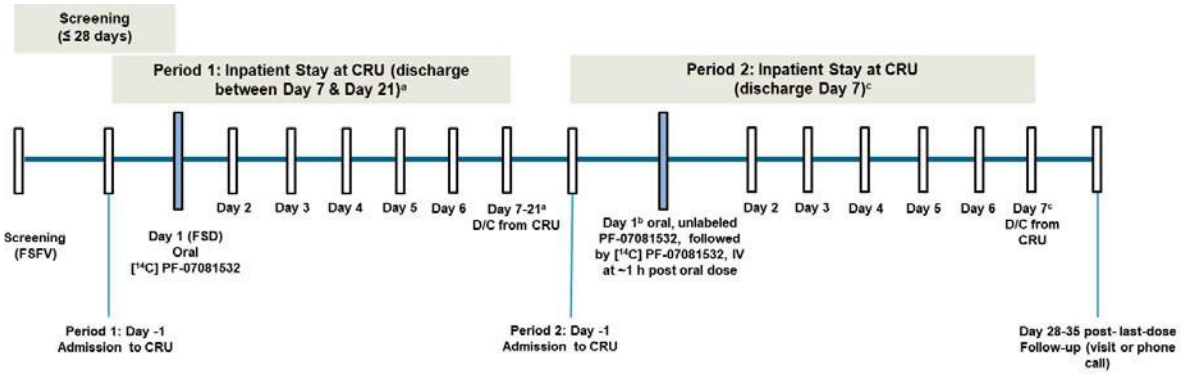
PK parameters (**Period 2**): Plasma PK parameters of [^{14}C]PF-07081532 will be calculated following administration of a single, IV, microdose of [^{14}C]PF-07081532.

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

Ethical Considerations:

Based on available clinical data with PF-07081532, a single 30 mg oral dose (Period 1), and a single 30 mg oral dose followed by 100 µg IV dose (Period 2) are anticipated to be safe and well tolerated. PF-07081532 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to evaluate the ADME properties of PF-07081532. Results from this study will inform and facilitate further clinical development of PF-07081532.

1.2. Schema



a. See Section 4.1 for details on Period 1 discharge criteria.
b. **At least 21 days** of washout is required between dosing in Period 1 and Period 2.
c. In Period 2, participants will be discharged from the CRU on Day 7.

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 Activities From Screening Through End of Period 1

Visit Identifier	Screen	Period 1																		ET
Day	gs	-1	1										2	3	4	5	6	7-213		
Hours After oral ^{14}C PF-07081532 Dose			0	0.5	1	2	4	6	8	10	12	15	24	36	48	72	96	120	144-480	
Infonned consent	X																			
COVID-19 testing /risk assessment[b]	*See ootnote*																			
Review of eligibility criteria	X	X																		
Inpatient stay at CRU		X																	X•	
Medical history																				
Review drug, alcohol/tobacco use		X																		X
Review prior & concomitant medications	X	X																		X
Physical examination[c]	X	X																	Xd	X
Supine 12-lead ECG			X																d	X
Supine vital signs (blood pressure and pulse rate)			X																d	X
Serious and non-serious adverse event monitoring																				
Standard meals[e]			e																	
Oral [^{14}C]PF-07081532 administration																				
CCI																				
Emesis collection for radioactivity measurement if occurs			X										X							
Blood samples for:																				
PK of PF-07081532				X							X	X	X	X					g	X
Total radioactivity	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	Xk	
Metabolite identificat[f011]			X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	xt	
Clinical laboratory tests after ≥4-hour fast	X	X																	Xd	X
Retained Research Sample prep D1[h]			X[h]																	
CCI																				
Urine samples for:																				
Urine drug testing	X	X																		
Spot collection for w analysis (and microscopy, if nee ded	X	X																		X
Total radioactivity and metabolite IDi		X	X					X		X		X	X	X	X	X		X		

Table 1. Schedule of Activities From Screening Through End of Period 1

Feces sam les for:								
Total fecal radioactivity and metabolite II)i	X	X	X	X	X	X	X	X

Note: for list of abbreviations refer to Appendix 11.

a. See Section 4.1 for details on Period 1 discharge criteria.

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

c. Complete physical examination, including height and weight, will be conducted at screening or admission of Period 1 only; brief physical exam at other time points, for findings during previous PE or new/open AEs, at investigator discretion.

d. Procedures to be perfom1ed on the day of discharge *only*. (see also Section 4.1).

e. Meals will be served throughout inpatient stay, as described in Section 5.3.2. Standardized meals to be served on Day 1.

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g. Samples to be collected up to the morning of Day 7 only.

h. 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.

1. "Blank" pre-dose urine sample to be collected v.rithin the 24 hours prior to dosing. Following oral dosing, each urine void to be collected across intervals of 0-12 hours, 12-24 hours, and each subsequent 24 hours interval up to discharge from Period 1, as described in Section 8.5.2.

J. "Blank" fecal sample to be collected from at least 1 bowel movement within the 48 hours prior to dosing, which may be collected from home. Following oral dosing, all feces excreted will be collected across each 24 hours interval up to discharge from Period 1, as described in Section 8.5.3.

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Table 2. Schedule of Activities From Period 2, Day -1 Through Follow-up

Visit Identifier	Period 2																					FU•	ET
Day	-1	1														2		3	4	5	6	7b	28-35	
Hours Relative to Oral Dosing of Unlabeled PF-07081532		0	0.5	1	1.17	1.25	1.33	1.5	2	4	6	8	10	12	**15**	24	36	48	72	96	120	144		
Hours Relative to Dosing of (^{14}C)PF-07081532 **(IV infusion start)**				0	0.17	0.25	0.33	0.5	1	3	5	7	9	11	**14**	**23**	**35**	47	**71**	**95**	**119**	**143**		
Inpatient stay at CRU	XC																							
COVID-19 testing/risk assessment'		*See footnote d*																						
Phvsical examinatiorl	X																					X		X
(Update.)dmg/alcohol/tobacco use	X•																						X	X
Review prior & concomitant medications	X•																						X	X
Supine 12-lead ECG		X																				X		X
Supine vital si=s (blood pressure and pulse rate)		X																				X		X
Serious and non-serious adverse event monitoring	X																					X	X	X
Standard mealsg		X								X			X											
Oral Unlabeled PF-07081532 administration		X																						
IV [^{14}C]PF-07081532 (administration as a 15 min infusion)				Xb		Xh																		
Blood samples for:																								
PK of PF-07081532		X	X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PK off^{14}ClPF-07081532				)Ci	X	XI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Clinical laborato1y after >4-hour fast	X																					X		X
Urine samples for:																								
Spot collection for minalysis (and microscopy, if needed)	X																					X		X
Total radioactivityi	Xi			X										X		X		X	X	X	X	X		
Fecal samples f01·:																								
Potential analysis of total radioactivity, [^{14}C]PF-07081532 and metabolite ID1:	XK			X												X		X	X	X	X	X		

Note: for list of abbreviations refer to Appendix 11.

a. Follow-up may be a phone call.
b. Pruticipants will be discharged on Day 7.

c. Participants will be admitted to the CRU on Day -1 of Period 2. At least 21 days washout is required between dosing in Period 1 and Period 2. If a participant in Period 1 is not discharged before Day 21, then the pruiicipant may continue directly to Period 2 (see also Section 4.1).
d. Assessment of risk for, symptoms of or testing for COVID-19 may be perfotmed at screening, admission to the CRU and/or at other times during the study at investigator discretion ru1d according to local site policies.
e. Will not be perfonned if the pa1ticipru1t was not discharged between Period **1** ru1d Period 2.
f. Brief physical exrun envisioned only for findings dming previous PE or new/open AEs, at investigator discretion.
g. Meals will be served throughout inpatient stay, as described in Section 5.3.2. Standardized meals to be served on **Day 1** of Period 2.
h. IV [^{14}C]PF-0708l 532 dose to be administered as an infusion over approximately 15 minutes (sta1ting at approximately 1 hour after the administration of the **oral** unlabeled PF-07081532 dose).
1. PK [^{14}C]PF-07081532 srunple at O hours to be collected immediately before the start of infusion; 0.25-hour sample to be collected immediately after the end of infusion.
J. Blank urine sample must be collected within the 24 hours prior to dosing. Following oral dosing, each urine void to be collected a.cross intervals of 1-12 hours (ie, post IV infusion), 12-24 hours, ru1d each subsequent 24 hour-interval up to dischru·ge from Period 2, as described in Section 8.5.2.
k. "Blank" fecal sample to be collected from at least 1 bowel movement during the 48 hours pre-dose interval, which may be collected from home. On Day 1 of Period 2 feces will be collected post IV infusion (ie, at 1-24 h following oral dosing) and thereafter across ea.ch subsequent 24-hour interval up to discharge from Period 2, as described in Section 8.5.3.

2. INTRODUCTION

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

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

2.1. Study Rationale

The purpose of the study is to assess the metabolism and extent of excretion of [^{14}C]PF-07081532 in urine and feces, following oral administration, in the fed state, in healthy male participants. This information will enable assessment of clearance mechanisms of PF-07081532 as well as identify disproportionate metabolites that should be qualified to adhere to the ICH M3 (R2) MIST guidance.[5] In addition, this study will characterize the fraction of dose absorbed and the bioavailability of orally administered PF-07081532, in the fed state, in reference to an IV dose of [^{14}C]PF-07081532. The characterization of absorption and oral bioavailability will enable BCS classification of PF-07081532. Finally, this study will also assess PK parameters following both oral and IV administration of [^{14}C]PF-07081532. The data collected in this study will enable further understanding of the ADME properties of PF-07081532.

2.2. Background

2.2.1. Nonclinical Pharmacology

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

2.2.2. Nonclinical Pharmacokinetics and Metabolism

CCI

[redacted]

CCI [redacted]

Fm1her details of the nonclinical phaimacokinetics and metabolism program are included in the IB.

2.2.3. Nonclinical Safety

The nonclinical safety profile of PF-07081532 has been adequately characterized to suppo1t progression into long-te1m clinical trials.

PF-07081532 was administered PO to Wistar-Han rats and cynomolgus monkeys in studies up to 6 and 9 months in dmation, respectively. PF-07081532 did not result in any mo1tality or adverse effects in any of the study parameters or endpoints evaluated. The NOAELs in the 6-month rat and 9-month monkey ivotal toxici studies were the hi est dose levels tested (100 m /k /da in both s ecies, CCI [redacted]

Studies were conducted to evaluate the effects of PF-07081532 on fertility, reproduction, and development in male and female rats, and EFD studies were conducted in rats and rabbits. No PF-07081532-related effects were observed in any male or female fe1tility or reproductive endpoints evaluated. The NOAELs for female fe1tility and early emb1yonic development and for male systemic toxicity and fe1tility were the highest doses evaluated and provide sufficient mai·gin over the highest planned clinical dose to suppo1t futme studies.

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

2.2.4. Clinical Overview

Two clinical studies (C3991001 and C3991002) have been completed with PF-07081532 in which a total of 88 participants have been randomized. Across these studies, 22 healthy adult paiticipants, 51 adult paiticipants with T2DM and 15 adult pa1ticipants with obesity have been randomized, with a total of 74 unique paiticipants exposed to at least I dose of PF-07081532.

One Phase 1 study, C3991003, is ongoing. This in-patient study to assess safety, tolerability and PK of multiple oral doses of PF-07081532 is emolling paiticipants with T2DM and paiticipants with obesity to receive PF-07081532 or placebo daily for 42 days. The staiting dose for the first coho1t enrolled in this study was 20 mg of PF-07081532, with subsequent dose levels dete1mined based on emerging data. While final clinical data from this study are not yet available, as of issuance of this protocol, there have been no deaths, SAEs, or AEs of severe intensity repo1ted.

2.2.4.1. Clinical Safety

The safety profile of PF-07081532 has been assessed in 2 completed clinical studies and, to date, administration of PF-07081532 at single doses up to 200 mg and multiple doses up to 180 mg QD over up to 42 days has been considered safe, with a tolerability profile consistent with the mechanism of action and a majority of TEAEs being mild in intensity and in the Gastrointestinal Disorders SOC.

Following single dose administration to healthy adult participants in study C3991001, the most frequently reported all-causality TEAEs across all treatment groups were nausea and vomiting, with an increased incidence of GI AEs noted at the dose of 200 mg. In the multiple ascending dose study, C3991002, the most frequently reported all causality TEAEs included nausea in participants with T2DM, and nausea and constipation in participants with obesity. Higher incidences of GI TEAEs were observed in the higher dose groups of PF-07081532 (120 mg QD and 180 mg QD) compared to placebo. There were no clinically significant adverse trends in safety laboratory tests, vital signs or ECG parameters in either study with increasing PF-07081532 doses.

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

CCI

[redacted]

2.3. Benefit/Risk Assessment

More detailed info1mation about the known and expected benefits and risks and reasonably expected AEs of PF-07081532, and the dmg class effects of marketed GLP-IR agonists, may be found in the IB which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significanc.e	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Inte1-vention PF-07081532		
Gastrointestinal adverse reactions	The potential risks are based on product labeling for injectable GLP-lR agonists (ie, liraglutide, exenatide, semaglutide and dulaglutide). Gastrointestinal adverse events, the majority of which were mild in intensity, have been observed in the clinical program with PF-07081532.	The single dose and dose level administered in this study minimize any potential risk.
Hypoglycemia	Clinical trials with injectable GLP-lR agonists have not demonstrated an increased risk for hypoglycemia. However, when administered in combination with anti-diabetic agents that are known to have an increased risk of hypoglycemia (such as insulin or sulfonylw-eas), an increased risk for hypoglycemia was observed.	The single dose and dose level administered in this study minimize any potential risk. The participants enrolled will not have diabetes and will not be receiving anti-diabetic agents. Study includes inpatient monitoring of the paiticipants following administration of a single dose of the study intervention.
Increased hea1t rate	Based on the product labeling for the injectable GLP-lR agonist liraglutide for obesity, mean increases in resting hea1t rate ranged 2 to 3 bpm in clinical trials, with some pa1ticipants experiencing greater increases in resting heart rate, up to 10-20 bpm.	The single dose and dose level administered in this study 1ninimize any potential risk. Study includes inpatient observation of the participants following administration of a single dose of the study intervention.
Potential risks associated with long-tenn dosing of marketed GLP-lR agonists include thyroid C-cell tumors, pai1creatitis, imoairment in renal function, diabetic	The potential risks are based on product labeling for injectable GLP-lR agonists (ie, liraglutide, dulaglutide, exenatide and semaglutide); additional info1mation is provided in the IB.	The single dose and dose level administered in this study 1ninimize any potential risk.

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

2.3.2. Benefit Assessment

PF-07081532 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to evaluate the ADME properties of PF-07081532. Results from this study will inform and facilitate further clinical development of PF-07081532.

2.3.3. Overall Benefit/Risk Conclusion

Based on available clinical data with PF-07081532 (Section 2.2.4 and current IB), a single 30 mg oral dose (Period 1), and a single 30 mg oral dose followed by 100 µg IV dose (Period 2) are anticipated to be safe and well tolerated. Each participant will be exposed to approximately 500 nCi over the entire study duration, which includes dosing [^{14}C]PF-07081532 in Period 1 and Period 2. This is classed as a microtracer dose, without any anticipated risk to study participants.

Based on the profile of PF-07081532 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 identified in association with PF-07081532 are justified by the anticipated benefits that may be afforded to participants with T2DM or obesity.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the extent of excretion of total radioactivity in urine, feces, and emesis (if any) following administration of a single oral dose of [^{14}C]PF-07081532.	• Total recovery of radioactivity in urine, feces, and emesis (if any), and both routes combined, expressed as a percent of total oral radioactive dose administered.
• To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of [^{14}C]PF-07081532.	• Metabolic profiling/identification and determination of relative abundance of [^{14}C]PF-07081532 and the metabolites of [^{14}C]PF-07081532 in plasma, urine, and feces.
Secondary:	**Secondary:**

• To quantify plasma PK parameters of PF-07081532 and total radioactivity following administration of a single oral dose of [^{14}C]PF-07081532.	• AUC_{last}, C_{max}, T_{max}, and if data permit, AUC_{inf}, $t_{½}$, CL/F (PF-07081532 only), and Vz/F (PF-07081532 only), to describe single oral dose PK in Period 1 of:
	  • Total radioactivity in plasma;
	  • PF-07081532 in plasma.

• To quantify plasma PK parameters of [^{14}C]PF-07081532, following administration of a single, IV, microdose of [^{14}C]PF-07081532.	• [^{14}C]PF-07081532 parameters to describe IV plasma PK: AUC_{last}, AUC_{last}(dn), C_{max}, C_{max}(dn), T_{max}, and if data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, CL, V_{ss} and MRT.
• To determine the absolute oral bioavailability (F) of PF-07081532 following administration of a single oral dose of PF-07081532 compared to a single IV microdose of [^{14}C]PF-07081532.	• F computed from plasma AUC_{inf} (if data permit, otherwise AUC_{last}) of oral unlabeled PF-07081532 in Period 2 and IV microdose of [^{14}C]PF-07081532 in Period 2.
• To determine the fraction of dose absorbed (F_a) following administration of a single oral dose of [^{14}C]PF-07081532.	• F_a calculated from ratio of total urinary radioactivity following oral administration of [^{14}C]PF-07081532 in Period 1 and IV administration of [^{14}C]PF-07081532 in Period 2.
• To evaluate safety and tolerability of PF-07081532, administered as a single oral dose of [^{14}C]PF-07081532 or a single oral dose of PF-07081532 followed by administration of a single IV microdose of [^{14}C]PF-07081532.	• Safety endpoints including physical examinations, adverse events, clinical laboratory measurements, vital signs, and ECG.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To characterize cumulative rate of excretion of total radioactivity in urine and feces over time following administration of a single oral dose of [^{14}C]PF-07081532.	• Cumulative recovery of radioactivity in urine and feces, and both routes combined over time as a percentage of total radioactive dose administered.
• To quantify plasma PK parameters of PF-07081532, following administration of a single oral dose of (unlabeled) PF-07081532.	• Parameters to describe oral plasma PK following oral administration of PF-07081532 in Period 2: C_{max}, C_{max}(dn), T_{max}, AUC_{last}, AUC_{last}(dn), and if data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, CL/F and V_z/F.
CCI [redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

C3991006 is a Phase 1, open-label, 2-period, fixed sequence study to characterize the metabolic profile and routes of excretion of oral [^{14}C]PF-07081532 and to evaluate the absolute oral bioavailability (F) and fraction absorbed (F_a) of PF-07081532 in healthy male participants.

Participants will be screened for enrollment in this study within 28 days of dosing on Day 1 of **Period 1**, to confirm that they meet the inclusion/exclusion criteria specified in Section 5. The expected duration of participation from screening to follow-up will be approximately 8 weeks (minimum) to approximately 12 weeks (maximum). The overall study design is summarized in Section 1.2 (Schema).

Regimen in Period 1: An oral dose of 30 mg PF-07081532 containing approximately 250 nCi [^{14}C] (ie, radiolabeled PF-07081532, [^{14}C]PF-07081532) will be administered within approximately 10 minutes of completion of a standard breakfast (see Sections 5.3.2 and 6.1.1).

Regimen in Period 2: An oral dose of 30 mg unlabeled PF-07081532 will be administered followed at approximate T_{max} by an IV dose of 250 nCi [^{14}C] in 100 µg of PF-07081532 (ie, [^{14}C]PF-07081532). The [^{14}C]PF-07081532 IV dose will be administered as an infusion over approximately 15 minutes, starting at approximately 1 hour (T_{max}) after the administration of the oral unlabeled PF-07081532 dose. Oral unlabeled PF-07081532 will be administered within approximately 10 minutes of completion of a standard breakfast (see Sections 5.3.2 and 6.1.1).

In Period 1, a sufficient number of participants will be admitted on Day -1 to the CRU to ensure that 6 participants are dosed on Day 1. Any participants who are prematurely withdrawn (or offer non-evaluable or partially evaluable data) will be replaced to ensure 6 evaluable participants completing Period 1. In Period 2, participants who are prematurely withdrawn may be replaced at the discretion of sponsor. Further details on "evaluable participants" will be provided in the SAP.

Discharge Criteria

In Period 1, participants may be discharged from the CRU on or after Day 7 when ***at least 1*** of the following criteria are met:

1. ≥90% of radioactive dose has been recovered in urine+feces+emesis (if any);
2. <1% of radioactive dose has been recovered in urine+feces during 24 hours interval over two consecutive days.

However, if neither of these 2 criteria are met and the participant has reached Day 21 in Period 1 they may be discharged prior to Period 2, or they may remain in the CRU until initiation of Period 2. If Period 1, Day 21 falls on the same day as Period 2, Day -1, for participants who have not been discharged from the CRU:

- Physical examination will not be performed on Period 1, Day 21.
- ECG and vital signs assessments will not be performed on Period 1, Day 21.
- Clinical laboratory (blood) and spot urine collection for urinalysis (and microscopy, if needed) assessments will be performed on Period 1, Day 21 and will serve as the Day -1 assessments of Period 2.
- The last urine sample for total radioactivity and metabolite ID collected up to 24 hours before dosing in Period 2 (ie, Period 1, Day 21) will serve as the Day -1 assessment of Period 2.
- The last fecal sample for total radioactivity and metabolite ID collected up to 48 hours before dosing in Period 2 (ie Period 1, Day 21 or Period 1, Day 20 if no bowel movement on Day 21) will serve as the Day -1 assessment of Period 2.

In Period 2, participants will be discharged from the CRU on Day 7.

At least 21 days of washout is required between dosing in Period 1 and Period 2. The participants may stay at the CRU during the washout period at the discretion of the investigator. Participants will have 1 follow-up contact (may be a phone call) that will occur at least 28 days and up to 35 days following the last dose of study intervention in Period 2.

4.2. Scientific Rationale for Study Design

A fixed sequence, open-label, study design has been chosen to minimize intra-individual variability and enable within-participant comparison of the urinary excretion of radioactivity with both oral and IV routes for the estimation of F_a. As is common for Phase 1 studies, the population envisioned for this study is healthy participants. 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.

Available PK data with PF-07081532 administered under fasted or fed conditions indicate that PF-07081532 may be administered without regard to food. In this study, dosing of PF-07081532 is planned to occur in the fed state, with standard breakfast in both periods, as described in Section 5.3.2, to reflect the conditions for anticipated use of PF-07081532 in future trials and the target patient population.

In this study, a "microtracer" approach will be used where the [^{14}C] dose is much lower than in conventional 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.

Period 1 of the study is designed to evaluate the metabolic fate and extent of excretion of PF-07081532 following 30 mg dose (250 nCi) via the intended clinical route of administration (oral) of [^{14}C]PF-07081532. In order to assess the metabolic fate of [^{14}C]PF-07081532, metabolites of [^{14}C]PF-07081532 circulating in plasma and eliminated in urine and feces following oral administration will be determined using AMS and UPLC-HRMS. Additionally, extent of excretion will be determined by recovery of total radioactivity excreted in urine and feces. Lastly, plasma PK of PF-07081532 will be compared to total radioactivity PK as an additional way to quantify circulating metabolites. Based on the half-life observed after single dose administration in Study C3991001 (mean ranging between 18 and 21 hours with individual values up to 29 hours), PF-07081532 is expected to be eliminated from plasma by Day 7 (144 hours). Additional 14 days of permitted extended stay in Period 1 (up to Day 21), based on predefined discharging criteria (see Section 4.1), is expected to be adequate to enable almost complete recovery of radioactivity in excreta and allow excretion of any potential metabolites with longer half-lives.

Samples for measurement of radioactivity in CCI will be collected in Period 1 at timepoints specified in the SoA. These samples may be assayed at sponsor's discretion to support any potential investigations in case of less than expected recovery of total radioactivity via urine and feces. Results from the analysis of these samples, if performed, may not be included in the CSR.

Period 2 of the study is designed to evaluate F and also allow to estimate F_a of the oral PF-07081532 dose. Determination of the Fa will provide information on the total PF-07081532 dose absorbed, regardless of the fate of that dose after absorption (eg, metabolism, degradation). Since F is dependent on F_a, F_g and F_h, characterization of both F and Fa will also enable determination of the first pass effect. A microdose (100 µg [250 nCi]) of [^{14}C]PF-07081532 will be administered as an IV infusion starting at the approximate T_{max} (1 hour) following an oral 30 mg dose of unlabeled PF-07081532. [^{14}C]PF-07081532 in plasma will be assessed via AMS following chromatographic separation. F will be calculated as the ratio of dose-normalized plasma AUC_{inf} following orally administered PF-07081532 to dose-normalized plasma AUC_{inf} following IV administered [^{14}C]PF-07081532. Administration of the IV microdose approximately at the T_{max} of the oral dose assures the presence of the appropriate total mass of drug material in the body so that PK data from the microdose (100 µg) can be scaled up to those measured following the higher oral dose (30 mg).

In Period 2, urine samples will be collected at prespecified intervals as described in the SoA and total radioactivity excreted in urine following IV administered [^{14}C]PF-07081532, will be measured via AMS. The ratio of dose-normalized total radioactivity recovered in urine following oral administration of [^{14}C]PF-07081532 in Period 1 to that recovered in urine following IV [^{14}C]PF-07081532 in Period 2 will provide an estimate of the F_a following oral administration. This F_a assessment assumes that the distribution, metabolism and excretion properties of PF-07081532 remain unchanged by the route of administration (oral or IV). Participants will be discharged from the CRU on Day 7 of Period 2, which is considered

adequate to meet study objectives and ensure that PF-07081532 has been eliminated from plasma. Even in the case that urine radioactivity recovery is not complete by Day 7 in Period 2 (after IV administration), it is expected that comparison with the urine radioactivity collected in Period 1 (after oral administration) over the same period of time (up to Day 7) will provide an adequate estimate of F_a.

Given that biliary and/or intestinal excretion is not expected to be a major clearance pathway of PF-07081532, feces in Period 2 will be collected but will be assayed at sponsor's discretion (if emerging data from the study indicate that contrary to current expectations, biliary and/or intestinal excretion may be a major clearance pathway or if for any other reason the study team determines that analysis of feces from Period 2 would further inform disposition of PF-07081532 in humans). Results from such analyses may or may not be included in the CSR, and should be interpreted with caution given that this study is not designed to achieve complete recovery of radioactivity in Period 2.

To aid in the future development of a potential pediatric dosage form of PF-07081532, the current study will assess the bitterness, tongue/mouth burn, and throat burn of the liquid formulation immediately after (within 3 minutes) and over 20 minutes post oral dose administration of [^{14}C]PF-07081532, in Period 1 only.

4.2.1. Choice of Contraception/Barrier Requirements

The potential risk of exposure to PF-07081532 in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations (See Appendix 4).[6]

4.2.2. Collection of Retained Research Samples

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

4.3. Justification for Dose

In C3991006, each participant will be exposed to approximately 500 nCi over the entire study duration, which includes dosing [^{14}C]PF-07081532 in Period 1 and Period 2. This is classed as a microtracer dose and based on precedent,[7,8] the doses of radioactivity used in this study are expected to result in adequate sensitivity for AMS quantification.

In **Period 1**, a single, oral dose of 30 mg of [^{14}C]PF-07081532 (250 nCi), will be administered. In Study C3991001, single ascending doses up to 200 mg were tested and were considered safe and had a tolerability profile in line with expectations for the mechanism of action, with the majority of AEs being mild in severity and in the Gastrointestinal Disorders SOC (with nausea and vomiting the most frequently observed). In that study, a single dose of

30 mg was very well tolerated with an AE profile that did not differ from placebo and with no treated participants experiencing vomiting up to that dose level (however, vomiting was observed at the 100 mg and 200 mg dose levels). Therefore, given the desire to minimize the risk of emesis in this study, a dose of 30 mg is considered appropriate. Given the early stage of development, there is still uncertainty around the efficacious dose range of PF-07081532 (doses spanning from 20 mg to 260 mg BID are currently planned to be investigated in Phase 2 efficacy studies). Since dose-proportional increases in exposure (AUC) of PF-07081532 have been observed after single dose (from 30 mg to 200 mg) and after multiple dose (from 10 mg to 180 mg QD), the results from this study can be extrapolated to doses exceeding 30 mg.

In **Period 2**, a single oral unlabeled 30 mg dose of PF-07081532 will be administered with food (standard breakfast), followed by an IV microdose of [^{14}C]PF-07081532, 100 µg (250 nCi) administered as infusion starting at the approximately expected T_{max} (1 hour) of the unlabeled oral dose. The IV microdose of 100 µg is ~0.3% of the oral dose of 30 mg and therefore expected to have negligible effect on the plasma PK of unlabeled PF-07081532, allowing for appropriate estimation of bioavailability. As per the ICH M3 (R2),[5] human administration of an IV microdose of up to 100 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 the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age and Sex:

1. Male participants must be 18 to 60 years of age, inclusive, at the time of signing the ICD.

- Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) participants.

2. Male participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, blood pressure and pulse rate measurement, standard 12-lead ECG, and laboratory tests.

Other Inclusion Criteria:

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

4. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures including collection of blank urine and feces samples prior to dosing on Day 1, Period 1.

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

   - Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

   - Positive testing at screening for HIV, HBsAg, HBcAb, HBsAb or HCVAb. Note: A positive HBsAb due to hepatitis B vaccination is permissible.

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

3. History of irregular bowel movements (eg, irritable bowel syndrome, frequent episodes of diarrhea, or constipation defined by less than 1 bowel movement on average per 2 days) or lactose intolerance.

4. Other medical or psychiatric condition including recent (within the past year of screening) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg, contact with positive case) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

5. Use of any prescription or non-prescription drugs and dietary and herbal supplements as outlined in Section 6.9 and Appendix 10.

Prior/Concurrent Clinical Study Experience:

6. Previous administration with an investigational product (drug or vaccine) within 90 days (or as determined by the local requirement) preceding the first dose of study intervention used in this study.

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

Diagnostic Assessments:

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

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

10. eGFR <90 mL/min/1.73m^2 (calculated with the 2021 CKD-EPI Scr only equation) at screening.

11. 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 the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

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

    - AST **or** ALT level ≥1.5 × ULN;

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

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

15. History of sensitivity to heparin or heparin-induced thrombocytopenia ***only if*** heparin is planned to flush IV catheters.

16. Total [^{14}C] radioactivity measured in plasma at screening exceeding 11 mBq/mL.

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

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.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

No contraception methods are required by the sponsor for male participants receiving PF-07081532. Please refer to Section 4.2.1 and Appendix 4.

5.3.2. Meals and Dietary Restrictions

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

- Participants must abstain from all food and drinks (except water) for at least 4 hours prior to any scheduled safety laboratory evaluations.

- Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

Dose administered with food, on Day 1 of Period 1 and Period 2:

- Following an overnight fast (abstain from all food and drink, except water) of at least 8 hours, prior to predose PK sample collection, a standard breakfast will be served.

- Participants should begin breakfast approximately 30 minutes prior to oral PF-07081532 administration. The breakfast will be consumed over approximately a 20 minute period with the study intervention administered approximately 10 minutes after completion of the meal. Participants will be encouraged to complete the entire breakfast.

  On **Day 1** of study **Period 1** and **Period 2**, the **same breakfast**, including food and beverage, should be served. Water may be consumed without restriction.

- On **Day 1** of both the study periods, lunch will be provided approximately 4 hours after oral administration of PF-07081532. Dinner will be provided approximately 10 hours after oral administration of PF-07081532. An evening snack may be permitted. If judged necessary by the investigator, participants may delay or skip a post-dose meal (lunch, dinner or snack) on dosing Day 1 in case of a gastrointestinal AE.

- Participants will refrain from consuming red wine, grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) and their 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.

- The nutritional macronutrient composition consumed by each participant should be maintained, as much as practically possible, during the inpatient stay.

- Ingestion of indigestible foods (eg, corn, nuts) should be avoided for 2 days prior to dosing and while inpatient to aid fecal homogenization.

- When a meal is scheduled at the same time as an ECG and/or vital sign assessments, the meal will be provided after the ECG and/or vital sign assessments are completed.

5.3.2.1. Dietary Fiber Supplementation

To help assure regularity in bowel movements, nutritional composition should include high fiber content (at least 15 g of fiber per 1000 kcal). ***This may include*** consumption of fiber (eg, capsules), at a frequency dictated by the investigator, starting with the evening meal (ie, approximately 10 hours post dose) on Day 1, for duration of inpatient stay to ensure at least 1 bowel movement per day.

If an individual participant has not experienced a bowel movement in the first 24 hours after dosing, water intake should be increased and prune juice should be offered during Day 2.

Despite these measures, if bowel movement does not occur, on Day 3 and each subsequent day, consideration should be given to administration of a mild laxative/stool softener (eg, milk of magnesia, docusate), at investigator's discretion.

5.3.3. Caffeine, Alcohol, and Tobacco

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

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

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

5.3.4. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 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 not be rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to PF-07081532 (either unlabeled or [^{14}C]PF-07081532).

6.1. Study Intervention(s) Administered

Study Intervention(s)			
Intervention Name	[^{14}C]PF-07081532	PF-07081532	[^{14}C]PF-07081532
Arm Name (group of participants receiving a specific treatment or no treatment)	Period 1	Period 2	Period 2
Type	Drug	Drug	Drug
Dose Formulation	Extemporaneously prepared liquid formulation	Extemporaneously prepared liquid formulation	Extemporaneously prepared liquid formulation
Unit Dose Strength(s)	NA	NA	NA
Dosage Level(s)	30 mg, single dose	30 mg, single dose	100 µg, single dose
Route(s) of Administration	Oral	Oral	IV infusion
Use	Experimental	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. Refer to the SAI	Provided centrally by the sponsor. Refer to the SAI	Provided centrally by the sponsor. Refer to the SAI
Packaging and Labeling	[^{14}C]PF-07081532 components will be supplied by Pfizer, as bulk API and, where necessary, bulk excipients for the manufacture of the [^{14}C] labeled oral liquid formulation	Unlabeled PF-07081532 will be provided by Pfizer as bulk powders for extemporaneous preparation	[^{14}C]PF-07081532 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
Current/Former Name(s) or Alias(es)	[^{14}C]PF-07081532	PF-07081532	[^{14}C]PF-07081532

Study Arm(s)		
Arm Title	Period 1	Period 2
Arm Type	Experimental	Experimental
Arm Description	Oral dose of 30 mg PF-07081532 containing 250 nCi [^{14}C] ([^{14}C]PF-07081532) will be administered as an extemporaneously prepared liquid formulation, approximately 10 minutes after completion of breakfast	Unlabeled oral dose of PF-07081532, 30 mg will be administered as an extemporaneously prepared liquid formulation, approximately 10 minutes after completion of breakfast. Approximately 1 hour after the administration of the unlabeled oral dose, a single dose of 100 µg PF-07081532 containing 250 nCi [^{14}C] ([^{14}C]PF-07081532) will be administered IV, as an infusion over approximately 15 minutes
Associated Intervention Labels	[^{14}C]PF-07081532	PF-07081532, [^{14}C]PF-07081532

6.1.1. Administration

In both periods, study intervention will be administered following breakfast, as described in Section 5.3.2, and according to the SAI.

In **Period 1**, oral dose of [^{14}C]PF-07081532, 30 mg (250 nCi) will be administered as an extemporaneously prepared liquid formulation, approximately 10 minutes after completion of breakfast.

In **Period 2,** unlabeled oral dose of PF-07081532, 30 mg will be administered as an extemporaneously prepared liquid formulation, approximately 10 minutes after completion of breakfast. Approximately 1 hour after the administration of the unlabeled oral dose, a single dose of [^{14}C]PF-07081532, 100 µg (250 nCi) will be administered IV, as an infusion over approximately 15 minutes.

Administration of labeled and unlabeled PF-07081532 via oral and IV 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.

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 by the sponsor.

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).

8. Further guidance and information for the final disposition of unused study interventions are provided by the sponsor. 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.

Unlabeled PF-07081532 and [^{14}C]PF-07081532 oral dosing formulations will be prepared in the CRU by 2 trained personnel and QP. Details of dose preparation will be given in a separate EDR. The 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-07081532 formulation for IV administration will be manufactured at the CRU by 2 trained personnel and QP-released prior to administration. Details of the dose preparation will be provided in a separate TA. The prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

6.3. Assignment to Study Intervention

Following completion of informed consent at the screening visit, each participant will be assigned an 8-digit SSID number, by the site staff. The first 4 digits of the SSID will reflect the sponsor-assigned site number and the remaining 4 digits will reflect each participant's unique number assigned in chronological order as informed consent is obtained. ***In addition***, on Day 1, each participant who is dosed with the study intervention will be assigned a separate, distinct number (as provided to the site by the sponsor at the start of the study) to enable execution of sponsors' standard processes for analysis of all PK-related samples.

6.4. Blinding

This is an open-label study.

6.4.1. Blinding of Participants

Participants will be unblinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

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

6.4.3. Blinding of the Sponsor

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

6.5. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. 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 oral dose of study intervention was ingested.

See the site administration instructions for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.6. Dose Modification

Dose modification of PF-07081532 is not permitted.

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-07081532 greater than 1.6 g within a 24-hour time period is projected to result in exposure that will exceed that observed at the NOAEL in the pivotal 9-month toxicology study in monkeys, after accounting for species difference in plasma protein binding, and thus will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

Use of any prescription or non-prescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention or as outlined in Appendix 10 specifically for medications prohibited due to potential DDI. Participants will abstain from all concomitant treatments during the study, except for the treatment of AEs. Limited use of non-prescription medications that are not believed to affect participant safety or the overall results of the study **may be permitted on a case-by-case basis following approval by the sponsor** and as long as they are not listed in Appendix 10. Use of dietary fiber supplementation, prune juice or non-prescription medications (eg, milk of magnesia, ducosate) specifically used as needed to promote bowel movement (see Section 5.3.2.1) is allowed at investigator's discretion and such use should be recorded. Acetaminophen/paracetamol may also be used at doses of ≤1 g/day.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

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

6.9.1. Rescue Medicine

There is no rescue therapy to reverse AEs observed with PF-07081532; standard medical supportive care must be provided to manage any AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following: safety, behavioral, compliance, or administrative reasons, or if the study is terminated by sponsor.

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

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

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

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

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

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

The total blood sampling volume for individual participants in this study is approximately 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

Not applicable.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

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

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

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in 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 IV 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 utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

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

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

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

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

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 5 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

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

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

8.3.5. COVID-19 Specific Assessments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4.1.1. Reporting SAEs to Pfizer Safety

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

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

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

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A 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.

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 on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure,

the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

8.4.10. Medication Errors

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

Medication errors are recorded and reported as follows:

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

Medication errors include:

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

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

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

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

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

8.5. Pharmacokinetics

Instructions for the collection and handling of biological samples (plasma, urine, fecal, emesis [if any], and CCI) will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. The blood samples collected at nominal time point of 10 minutes and 15 minutes **post start** of IV infusion, will not be considered as a PD if it is collected within ±2 minutes of nominal time post start of infusion. **Note**: The 15-minute sample should **not** be collected prior to end of infusion. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

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

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

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

8.5.1. Analysis of Plasma

8.5.1.1. Period 1 Plasma Analysis of PF-07081532 Using LC/MS/MS

During **Period 1**, at each specified time-point in the SoA, blood samples (3 mL for LC/MS/MS analysis of PF-07081532) to provide approximately 1.2 mL plasma will be collected into appropriately labeled tubes containing K_2EDTA.

Samples for unlabeled PF-07081532 will be analyzed using a validated LC/MS/MS method in compliance with Pfizer standard operating procedures.

8.5.1.2. Period 1 Plasma Analysis of Total Radioactivity [^{14}C] Using AMS

During **Period 1**, at each specified time-point in the SoA, blood samples (4 mL for total radioactivity [^{14}C]) to provide approximately 1.6 mL plasma will be collected into appropriately labeled tubes containing K_2EDTA. For the pre-dose sample **only**, the blood volume collected is 10 mL.

8.5.1.3. Period 1 Plasma Analysis for Metabolite Profiling Using AMS and UPLC-HRMS

During **Period 1**, at each specified time-point in the SoA, blood samples (10 mL for metabolite identification) to provide approximately 4 mL plasma will be collected into appropriately labeled tubes containing K_2EDTA.

Plasma samples in **Period 1** will be analyzed using AMS and UPLC-HRMS, and will provide metabolite profile of [^{14}C]PF-07081532. Samples collected for plasma analysis of total [^{14}C] or PF-07081532 may also be analyzed for metabolite profiling at the discretion of the sponsor.

8.5.1.4. Period 2 Plasma for Analysis of Oral, Unlabeled PF-07081532, Using LC/MS/MS

For **Period 2**, blood samples (3 mL) to provide approximately 1.2 mL plasma for concentrations of unlabeled PF-07081532 will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the SoA.

Samples for unlabeled PF-07081532 will be analyzed using a validated LC/MS/MS analytical method in compliance with Pfizer standard operating procedures.

8.5.1.5. Period 2 Plasma for Analysis of IV [^{14}C]PF-07081532 Using AMS and UPLC-HRMS

During study **Period 2**, blood samples (4 mL) to provide approximately 1.6 mL plasma will be collected as specified in the SoA following IV administration of [^{14}C]PF-07081532, into appropriately labeled tubes containing K_2EDTA. Samples from **Period 2** will be analyzed for [^{14}C]PF-07081532 using a validated quantitative AMS method following chromatographic separation of the parent drug.

8.5.2. Analysis of Urine

In **Period 1** and **Period 2**, urine will be collected at time intervals specified in SoA (Table 1 and Table 2 respectively) to analyze the amount of total radioactivity eliminated in urine following oral and IV administration of [^{14}C]PF-07081532, respectively. Additionally, urine from Period 1 will be assessed for metabolite identification following oral administration of [^{14}C]PF-07081532.

- Prior to dosing on Day 1 (within 24 h), each participant must empty his urinary bladder; an aliquot from this urine will serve as the “urine blank”.
- Following dosing on Day 1, each void post dose will be collected and saved in a container and stored in refrigerated conditions (ie, 2-8°C) for the duration of the collection interval. Urine collection timings should be recorded in the CRF.
- At the end of the collection interval, participants must complete a forced void, with this void included as part of the interval collection.
- If the end of urine collection interval coincides with a meal, participants will be asked to complete the forced void prior to initiation of the meal; in such cases, so long as the actual time of forced void is recorded, for practical reasons, the fact that this collection may be more than 30 minutes (and up to 45 minutes) prior to end of collection interval is acceptable and will not be considered as protocol deviation.
- At the end of each urine collection interval, the urine container will be mixed thoroughly and the total weight of urine collected during the interval will be measured and recorded. All urine aliquots should be collected using a new pipette tube for each participant at each time point. All urine samples within each collection

interval will be mixed thoroughly before aliquoting. The details regarding the collection (eg, aliquots volume), processing, storage and shipping of the urine samples will be provided in the laboratory manual. Following completion of radioanalysis and sub-sample collections for metabolite profiling, the remaining aliquoted urine samples will be discarded upon approval from the sponsor.

8.5.3. Analysis of Feces

Feces will be collected in **Period 1** and **Period 2** at intervals specified in the SoA (Table 1 and Table 2 respectively). Feces collected in **Period 1** will be analyzed for total [^{14}C] and assessed for identification of metabolites at intervals prespecified in the SoA. Fecal samples in Period 2 may be analyzed for total [^{14}C] and/or [^{14}C]PF-07081532 and may be assessed for identification of metabolites if the study team determines that such analyses would further inform disposition of PF-07081532 in humans (see Section 4.2).

A pre-dose fecal sample is required within 48 hours prior to dosing [14C]PF-07081532 in Period 1 and Period 2. 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 samples will be discarded. Total fecal mass is to be recorded for each collection interval. Time and date of each bowel movement must be recorded. Additionally, all toilet paper that comes in contact with the participant's feces should also be collected in separate containers from the fecal samples for possible analysis. Fecal voids as per SoA will be collected and labeled at the clinic and immediately frozen at approximately -20°C. Fecal samples collected at home (pre-dose) will be labeled and stored at -20°C after participant enters the clinic.

In the event of diarrhea during the study, all diarrhea, including any swabbing and contaminated linen, should be collected, labeled, and stored in appropriate containers at -20°C for possible analysis of radioactivity. Following completion of radioanalysis and subsample collections for metabolite profiling, the remaining bulk fecal homogenate will be discarded upon approval from the sponsor.

8.5.4. Emesis Collection

If emesis occurs within 24 hours after oral administration of [^{14}C]PF-07081532 (**Period 1 only**), then the vomitus must be collected and stored for radioactivity assessment. All emesis including any swabbing, contaminated linens and facial tissues used to collect bodily discharge eg, nose bleeding clean-up tissue and any emesis related clean-up is to be collected and stored in a labeled emesis container at 4°C for possible analysis of radioactivity.

CCI [redacted]

8.5.6. Analysis of Dosing Formulation and Determination of Administered Dose

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 IV administration of [^{14}C]PF-07081532, the dose volume administered to individual participants will be controlled using pre-calibrated infusion pumps. Volume of IV dose (computed using weight of the dosing solution administered and the density of the dosing solutions), and concentration of PF-07081532 and radioactivity in dosing solution will be used to determine the exact dose administered for each participant.

The actual doses administered will be recorded in the CRF and will be used for calculating PK parameters as described in Section 8.10.

Details on administration of dose and amount of doses administered in Period 1 and Period 2 will be described in the SAI and the laboratory manual.

8.6. Genetics

CCI

[redacted]

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.

CCI

[redacted]

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypothesis

No statistical hypothesis will be tested in this study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to and dosing with study intervention. 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.
Safety analysis set	All participants assigned to study intervention and who take at least 1 dose of study intervention.

Participant Analysis Set	Description
Extent of excretion analysis set	In Period 1, extent of excretion population will be defined by evaluable participants who have received 1 dose of [^{14}C]PF-07081532 and who have complete total radioactivity concentration (urinary and fecal) data and who had no protocol deviations that may have affected the extent of excretion analysis. Further details will be provided in the SAP, where, notably, vomiting within 24 hours post oral dose does not necessarily preclude participants as non-evaluable.
PK concentration set	The PK concentration population for PF-07081532 is defined as all participants dosed with PF-07081532 or [^{14}C]PF-07081532, who have at least one PF-07081532 concentration. The PK concentration population for [^{14}C]PF-07081532 is defined as all participants dosed with [^{14}C]PF-07081532, who have at least one [^{14}C]PF-07081532 measurement. The PK concentration population for total [^{14}C] is defined as all participants dosed with [^{14}C]PF-07081532, who have at least one total [^{14}C] measurement.
PK parameter set	The PK parameter analysis population for PF-07081532 is defined as all participants dosed with PF-07081532 or [^{14}C]PF-07081532 who have at least one of the PF-07081532 PK parameters of interest. The PK parameter analysis population for [^{14}C]PF-07081532 is defined as all participants dosed with [^{14}C]PF-07081532 who have at least one of the [^{14}C]PF-07081532 PK parameters of interest. The PK parameter analysis population for total [^{14}C] is defined as all participants dosed with [^{14}C]PF-07081532 who have at least one of the total [^{14}C] PK parameters of interest.

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. General Considerations

This section will be described in detail in the SAP.

9.3.2. Primary Endpoint(s) Analysis

9.3.2.1. Extent of Excretion (Period 1)

Radioactivity excreted in urine and/or feces will be reported as the percentage of the administered radioactivity excreted at each time interval, cumulatively through that interval and the total percent of dose recovered in urine, feces, and/or emesis (if any).

Percent recovery and cumulative recovery of total radioactivity in urine, feces and emesis (if any) will be determined based on total administered dose.

Note: While the total percentage of dose excreted is the primary endpoint, the percentage of the administered radioactivity excreted at each time interval and cumulatively through that interval are tertiary endpoints.

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 in **Period 1 only**. Emesis, if any, will be collected during 24 hours post oral dose, but these participants will not necessarily be excluded from analysis (see Section 9.3 for additional details on evaluable participants). The total recovery of radioactivity in urine, feces (and emesis, if any) and their combination will be listed and summarized for **Period 1 only**.

9.3.2.2. Metabolite Profiling and Metabolite Identification (Period 1)

Plasma, urine and fecal samples collected in Period 1 will be analyzed for metabolites of PF-07081532. Major metabolites of PF-07081532 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. Results of the metabolic profiling analysis will be detailed in a separate report and will be summarized within the CSR.

9.3.3. Secondary Endpoint(s) Analysis

9.3.3.1. Pharmacokinetic Parameters

9.3.3.1.1. Plasma

- For **Period 1**, following a single oral administration of [^{14}C]PF-07081532, oral PK parameters for total [^{14}C] radioactivity will be derived from the concentration equivalent-time profiles, where appropriate. Additionally, PK parameters for PF-07081532 will be derived from the concentration-time profiles based on LC/MS/MS analysis of plasma samples.

- For **Period 2**, following a single oral dose of unlabeled PF-07081532, PK parameters for PF-07081532 will be derived from the concentration-time profiles based on LC/MS/MS analysis of plasma samples (note that this reflects a tertiary endpoint and as such is also listed under Section 9.3.4).

- For **Period 2**, following a single IV microdose dose of [^{14}C]PF-07081532 at 1 hour post oral dose, IV plasma PK parameters of [^{14}C]PF-07081532 will be derived from plasma radioactivity concentration-time profiles following chromatographic separation of [^{14}C]PF-07081532.

Parameter	Definition	Method of Determination
AUC_{last}	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 Period 2 only	AUC_{last}/Dose
AUC_{inf}[a]	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis, 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 zero extrapolated to infinite time, in Period 2 only	AUC_{inf}/Dose
C_{max}	Maximum plasma concentration	Observed directly from data
C_{max}(dn)	Dose-normalized maximum plasma concentration, in Period 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 following IV administration	Dose/AUC_{inf}
MRT[a] (IV)	Mean residence time	$AUMC_{inf}/AUC_{inf}$ - (infusion time/2)
V_{ss}[a] (IV)	V_{ss}: Steady-state volume of distribution following IV administration	$V_{ss} = CL \times MRT$
CL/F[a] (oral)	Apparent clearance of PF-07081532 following oral administration	Dose/AUC_{inf}
V_z/F[a] (oral)	Apparent volume of distribution of PF-07081532 following oral administration	Dose /($AUC_{inf}*k_{el}$)

[a] If data permit.

Actual PK sampling times will be used in the derivation of PK parameters, defined relative to the time of the oral dose for the parameters referring to oral dosing and relative to the start of the 15-minute IV infusion for the parameters referring to IV dosing. Actual administered [^{14}C] doses will be used for the total [^{14}C] and [^{14}C]PF-07081532 PK parameter calculations.

Plasma PK parameters above will be listed and summarized descriptively as appropriate, by analyte (total [^{14}C], unlabeled PF-07081532, and [^{14}C]PF-07081532) and route of administration (oral or IV), as specified in the SAP.

Individual participant profiles of the concentration-time data will be plotted by analyte and route of administration using the actual PK sampling times. Summary plots (median and mean) of the concentration-time data will be presented for each analyte and for route of administration using the nominal PK sampling times.

Plasma concentrations/concentration equivalents for each of the analytes will be listed and summarized descriptively by nominal PK sampling time and route of administration.

9.3.3.1.2. Absolute Bioavailability

F will be estimated (in **Period 2** only) as the ratio of adjusted geometric means of dose-normalized AUC_{inf} (if data permit, otherwise AUC_{last}) following oral, unlabeled, PF-07081532 and IV, [^{14}C]PF-07081532 which is equivalent to the following equation:

$$F = [PF\text{-}07081532\_AUC_{po}/PF\text{-}07081532\_AUC_{iv}]*[PF\text{-}07081532\_Dose_{iv}/PF\text{-}07081532\_Dose_{po}]$$

Natural log transformed AUC_{inf}(dn) (if data permit, otherwise AUC_{last}(dn)) from **Period 2** will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted (least squares) mean differences (Test-Reference) and the corresponding 90% confidence interval 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 means (Test/Reference) and 90% confidence interval for the ratio where IV [^{14}C]PF-07081532 is the reference formulation and unlabeled oral PF-07081532 is the test formulation.

Summary plasma concentrations (dose-normalized) of orally administered PF-07081532 and IV administered [^{14}C]PF-07081532 in Period 2 will be presented in the same plot by route of administration using nominal sampling times.

9.3.3.1.3. Fraction Absorbed

9.3.3.1.3.1. Urine Parameters

The following urine parameters will be calculated following single dose administration of a microtracer dose of [^{14}C]PF-07081532 (oral and IV administration), as data permit. Residual [^{14}C] levels from Period 1 will be accounted for using an appropriate method, based on AMS principles and methodology.

Parameter	Definition	Method of Determination
Total [^{14}C]_Urine_PO	Total cumulative radioactivity excreted into urine from time zero up to the time of last measurable concentration following oral administration of [^{14}C]PF-07081532 (**Period 1** only)	Directly from observed [^{14}C] data, calculated as sum of [^{14}C urine concentration × sample volume] for each collection interval
Total [^{14}C]_Urine_PO_Trunc*	Total cumulative radioactivity excreted into urine from time zero up to Day 7 (matching duration of Period 2 urine collection up to discharge) following oral administration of [^{14}C]PF-07081532 (**Period 1** only)	Directly from observed [^{14}C] data, calculated as sum of [^{14}C urine concentration × sample volume] for each collection interval
Total [^{14}C]_Urine_IV	Total cumulative radioactivity excreted into urine from time zero up to the time of last measurable concentration following IV administered [^{14}C]PF-07081532 microdose (**Period 2** only)	Directly from observed [^{14}C] data, calculated as sum of [^{14}C urine concentration × sample volume] for each collection interval
% [^{14}C]_Urine_PO	% of radioactivity in the urine following oral administration, expressed as a percent of the radioactive dose administered (**Period 1** only)	(Total [^{14}C]_Urine_PO/[^{14}C] $Dose_{po}$) *100 where, [^{14}C] $Dose_{po}$ is orally administered actual dose of [^{14}C]PF-07081532
% [^{14}C]_Urine_PO_Trunc*	% of radioactivity in the urine up to Day 7 (matching duration of Period 2 urine collection up to discharge) following oral administration, expressed as a percent of the radioactive dose administered (**Period 1** only)	(Total [^{14}C]_Urine_PO_Trunc/[^{14}C] $Dose_{po}$) *100 where, [^{14}C] $Dose_{po}$ is orally administered actual dose of [^{14}C]PF-07081532
% [^{14}C]_Urine_IV	% of radioactivity in the urine following IV administration expressed as a percent of the radioactive dose administered (**Period 2** only)	(Total ^{14}C _Urine_IV/[^{14}C] $Dose_{iv}$) *100 where, [^{14}C] $Dose_{iv}$ is [^{14}C] IV administered actual dose of [^{14}C]PF-07081532

*_Trunc parameters may not be calculated and reported if not applicable (ie, no participant is discharged after Day 7 in Period 1).

The above parameters will be listed and summarized using descriptive statistics, as specified in the SAP.

9.3.3.1.3.2. Calculation of F_a

F_a will be estimated as the ratio of adjusted geometric means of the % of administered radioactive dose excreted into urine following oral and IV administration of [^{14}C]PF-07081532 in **Periods 1 and 2**, respectively. Urine radioactivity up to Day 7 will be used for Period 1 to match the duration of Period 2 urine collection up to discharge:

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

Natural log transformed % [^{14}C]_Urine_PO_Trunc (if data permit) from Period 1 and % [^{14}C]_Urine_IV (if data permit) from Period 2 will be analyzed using a mixed effect model with treatment as a fixed effect and participant as a random effect. Estimates of the adjusted (least squares) mean differences (Test-Reference) and the corresponding 90% confidence interval 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 means (Test/Reference) and 90% confidence interval for the ratio where IV [^{14}C]PF-07081532 is the reference formulation and oral [^{14}C]PF-07081532 is the test formulation.

9.3.3.2. Safety Analyses

All safety analyses will be performed on the safety population.

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

Medical history and 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 and [^{14}C] measurements collected at screening will be reported.

9.3.3.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized by treatment and time.

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

Safety QTcF Assessment

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

In addition, the number of participants with uncorrected QT values >500 ms will be summarized.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

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[redacted]

9.3.4.2. Cumulative Rate of Excretion (Period 1)

See Section 9.3.2.1.

9.3.4.3. Pharmacokinetics Parameters (Oral Unlabeled PF-07081532 - Period 2)

See Section 9.3.3.1.1.

9.3.5. Other Analyses

Details on the analysis of data derived from the collected CCI [redacted] samples (if assayed) will be provided in the SAP. Results of such analyses (if performed) may not be included in the CSR.

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

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. 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 modeling, and/or supporting clinical development.

9.5. Sample Size Determination

A sample size of approximately 6 participants has been chosen based on the industry standard sample size for mass balance and radiolabeled microtracer studies and in line with latest FDA draft guidance (May 2022).[9] This sample size was not chosen based on any empirical data or hypothesis testing criteria. The sample size has been selected to ensure that 6 participants provide evaluable data after completing Period 1; with intent to replace participants who prematurely withdraw (or offer non-evaluable or partially evaluable data). In Period 2, participants who are prematurely withdrawn may be replaced at the discretion of sponsor.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

10.1.5. Committees Structure

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

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 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring 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 source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) 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. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered

closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.10. Publication Policy

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

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

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide

comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

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

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, 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 3. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine (Scr) Cystatin C (Scys) on Day -1 only eGFR[a] ***Serum*** Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (Bicarbonate) AST ALT Alkaline phosphatase GGT T bili Direct bilirubin[b,c] Indirect bilirubin[b,c] Creatine kinase[b,d] Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[e]	Other tests as part of clinical laboratory tests: COVID-19 test[f] At screening only: • Serology: HBsAg, HCVAb (if positive, HCV RNA) and HIV At screening and Day -1 only: • Urine drug test[g] For suspected DILI: • AST, ALT • T bili, direct and indirect bilirubin • Total bile acids, GGT • Albumin • Alkaline phosphatase • CK • PT, INR • Acetaminophen/paracetamol or protein adduct levels For suspected DICI/DIKI: Creatinine (Scr) Cystatin C (Scys)[h] eGFR[h] UACR

a. eGFR should be calculated using the 2021 CKD-EPI Scr only equations, see Appendix 7.
b. At screening and Day -1 ***only,*** unless conditions for testing are met after Day 1 per notes "c" and "d" below.
c. After Day 1, direct and indirect bilirubin assessed only when T bili is > ULN.
d. After Day 1, creatine kinase assessed only when ALT is > ULN.
e. If abnormal urine dipstick results including positive results for blood, protein, nitrites or leukocyte esterase.
f. Assessment of risk for, symptoms of or testing for COVID-19 may be performed at screening, admission to the CRU and/or at other times during the study at investigator discretion and according to local site policies.
g. Minimum testing requirements include cocaine, THC, opiates, barbiturates, benzodiazepines and amphetamines (including XTC).
h. For suspected DICI/DIKI, reflex measurement of Scys will be conducted and eGFR will be calculated using both the 2021 CKD-EPI Scr only and the 2021 CKD-EPI Scr-Scys Combined equations, see Appendix 7.

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, unexpected safety findings, or other exploratory purposes. 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 occmTence 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 abnonnal laborat01y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

• Any abnormal laborato1y test results (hematology, clinical chetnistty, or minalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measmements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnonnal laborat01y 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/smgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjusttnents) or discontinuation from the study, significant additional concotnitant dmg tt-eattnent, or other therapy.
 	
• Exacerbation of a chronic or intennittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study inte1vention adtninistt·ation, even though it may have been present before the sta1t of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected dmg-dmg interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study inte1vention or a concotnitant medication. Overdose per se will not be repo1ted as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-hanning intent. Such overdoses should be repo1ted regardless of sequelae.

Events	Meeting the AE Definition
	• Any clinically significant abno1mal laborato1y findings or other abnonnal safety assessments that are associated with the underlying disease, lmless judged by the investigator to be more severe than expected for the pa1ticipant'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 pa1ticipant's condition. • Medical or smgical procedme (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occmTence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the sta1t 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 tenn "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 tnight have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the paiticipant has been adtnitted (usually involving at least an overnight stay) at the hospital or emergency wai·d for obse1vation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization ai·e AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occmTed or was necessa1y, 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 tenn disability means a substantial disrnption of a person's ability to conduct nonnal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diaIThea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent eve1yday life functions but do not constitute a substantial disrnption.

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 laborat01y findings indicating an infection in a pa11icipant exposed to a Pfizer product. The te1ms "suspected transmission" and "transtnission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by phatmacovigilance 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 patticipant 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.
- Exainples 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 dtug dependency or dtug 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 sUllllnat·izes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Repo11 Fotm to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

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

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

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

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Repo1i Fonn/AE or SAE CRF page.

- There may be instances when copies of medical records for ce1iain cases are requested by Pfizer Safety. In this case, all paiiicipant identifiers, with the exception of the paiiicipant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE repo1ied during the study and assign it to I 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 usualADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomf01i, but poses no significant or permanent risk of haim to the research pa1iicipant.

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

An event is defined as "serious" when it meets at least I 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 inte1vention and each occunence of each AE or SAE. The investigator will use clinical judgment to dete1mine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be rnled out.

- Alternative causes, such as underlying disease(s), 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 infonnation, 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 occmTed and the investigator has minimal infonnation to include in the initial repo1t to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change their opinion of causality in light of follow-up info1mation and send an SAE follow-up repo1t with the updated causality assessment.

- The causality assessment is one of the criteria used when dete1mining regulato1y 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 repo1ting pmposes, as defined by the sponsor. In addition, if the investigator dete1mines that an SAE is associated with study procedmes, the investigator must record this causal relationship in the somce documents and CRF, and repo1t such an assessment in the dedicated section of the CT SAE Repo1t Fo1m and in accordance with the SAE repo1ting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perfo1m or aITange for the conduct of supplemental measmements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the natme and/or causality of the AE or SAE as fully as possible. This may include additional laborato1y tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a paiticipant dies dming paiticipation in the study or dming a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmo1tem findings, including histopathology.

- New or updated infom1ation 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 info1mation.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primaiy mechanism for repo1iing an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to rep01i the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper f01m (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entiy of new data or changes to existing data.
- If a site receives a repo1i of a new SAE from a study pa1iicipant or receives updated data on a previously reported SAE after the electi·onic DCT has been taken off-line, then the site can repo1i this info1mation on a paper SAE f01m (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile ti·ansnussion of the CT SAE Report Fonn is the prefened method to ti·ansmit 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 Repo1i Fo1m sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Fo1m pages within the designated repo1iing time fraines.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

As the calculated safety margin between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies is ≥100-fold (see Section 4.2.1), no contraception methods are required by the sponsor for male participants receiving PF-07081532.

If more conservative guidelines on contraception are required (for example, per local regulations or IRBs/ECs) the male participants in this study may be asked to use contraception. In such cases, full detail will be provided in the informed consent document.

10.4.2. Female Participant Reproductive Inclusion Criteria

Not applicable.

10.4.3. Woman of Childbearing Potential

Not applicable.

10.4.4. Contraception Methods

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

CCI

[redacted]

[redacted]

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

    - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

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

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

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

10.7.2. Age-Specific Kidney Function Calculation Recommendations

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

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

Inker LA et al. N Engl J Med. 2021;385:1737-49.[10]

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

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

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

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

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 ms.
- New prolongation of QTcF to >480 ms (absolute) or by 60 ms from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of>30 seconds' duration.
- Frequent PVCs, triplets, or sho1t intervals (<30 seconds) of consecutive ventricular complexes.

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

- QTcF prolongation >500 ms.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset LBBB (QRS complex>l20 ms).
- New-onset right bundle branch block (QRS complex>120 ms).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free pa1ticipants in sinus rhythm, with documented periods of asystole 3 .0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained"= sho1i duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' dmation, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR> I00 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heait block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyaIThythmias (>30 seconds' dmation).
- 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 aIThythmia classified as an adverse expenence.

The enumerated list of major events of potential clinical concem are re commended as "aletts" or notifications from the core ECG laborato1y to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be repotted as AEs/SAEs.

CCI

[redacted]

CCI

[redacted]

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[redacted]

10.10. Appendix 10: Prohibited Concomitant Medications That May Result in DDI

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

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

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

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

Investigators should consult the product label for any other medication used during the study for info1mation regarding medication that is prohibited for concomitant use.

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

Drug Category	Drugs (Therapeutic Class)	Washout Period Requirement Prior to the First Dose of Study Intervention
	Ribociclib (Kinase Inhibitor), Ritonavir (Protease Inhibitor), Saquinavir (Protease Inhibitor), Saquinavir and Ritonavir (Protease Inhibitor), Telaprevir (Antiviral), Telithromyci..11(Antibiotic), Tipranavir and Ritonavir (Protease Inhibitor), Troleandomycin(Antibiotic), Tucatinib (Kinase Inhibitor), Ombitasvir and Paritaprevir and Ritonavir and Dasabuvi.I·(Antiviral), Voriconazole (Antifungal)	
CYP3A Inducer (strong)	Apalutamide (Antianclrogen), Avasimibe (Antilipemic), Carbamazepine (Anticonvulsant), Enzalutamide (Antiandrogen), Ivosidenib (Cancer Treatment), Lumacaftor (Cystic Fibrosis Treatment), Mitotane (Antineoplastic), Phenytoin (Anticonvulsant), Rifampin (Antibiotic), RifapentiI1e (Antibiotic), St. John's wo1t extract (Herbal Medication)	5 half-lives plus 14 days
CYP3A Inducer (moderate)	Aslllaprevir and Beclabuvir and Daclatasvi.I· (Antiviral), Bosentan (Endothelill Receptor Antagonist), Cenobamate (Anticonvulsant), Dabrafenib (Ki..11ase Inhibitor), Efavirenz (Non-nucleoside Reverse Transcriptase Inhibitor), Elagolix (Gonadotropin-releasillg Ho1mone Receptor Antagonist), Etravirille (Non-nucleoside Reverse Transcriptase Inhibitor), LersiviriI1e (Non-nucleoside Reverse Transcriptase Inhibitor), Lenisurad (Antigout and Uricosuric Agent), Lopinavir (Protease Inhibitor), Lorlatillib (Ki..11ase Inhibitor), Metamizole / Dipyrone (Analgesic), Mitapivat (Pymvate Killase Activator), Modafinil (Psychostimulant), Nafcillill (Antibiotic),	5 half-lives plus 14 days

Drug Category	Drugs (Therapeutic Class)	Washout Period Requirement Prior to the First Dose of Study Intervention
	Pexida1tinib (Kinase Inhibitor), P1imidone (Anticonvulsant), PF-06282999 (Myeloperoxidase Inactivator), Phenobarbital (Anticonvulsant), Rifabutin (Antibiotic), Semagacestat (Alzheimer's Disease & Dementia Treatment), Sotorasib (Kinase Inhibitor), Talviraline (Non-nudeoside Reverse Transcriptase Inhibitor), Telotristat Ethyl (Antidianheal), Thioridazine (Antipsychotic), Tipranavir and Ritonavir (Protease Inhibitor)	
OATP (1Bl/1B3) Inhibitor	Atazanavir and Ritonavir (Protease Inhibitor), Boceprevir (Antiviral), Clarithromycin (Antibiotic), Cyclospoiine (Immunosuppressant), Eltrombopag (Thrombopoietin receptor agonist) Elythromycin (Antibiotic), Faldaprevir (Antiviral), Gemfibrozil (Fibric Acid Derivative), Grazoprevir (Antiviral), Itraconazole (Antifungal), Lete1movir (Antiviral), Lopinavir and Ritonavir (Protease Inhibitor), Rifampin, single dose (Antibiotic), Simeprevir (Antiviral) Telaprevir (Antiviral), Velpatasvir (Antiviral)	14 days or 5 half-lives, whichever is longer
CYP2C19 Substratea	BMS-823778 (Diabetes Treatment), Clobazam (Benzodiazepine), Clopidogrel (Antiplatelet),b Diazepam (Benzodiazepine), Gliclazide (Sulfonylurea), Hexobarbital (Hypnotic - Sedative), Mephobarbital (Anticonvulsant), Proguanil (Antimalarial), S-mephenytoin (Anticonvulsant), Tilidine (Treatment of Pain & Inflammation), Valproic acid (Anticonvulsant)	14 days or 5 half-lives, whichever is longer
UGTIAI Substrate	Belinostat (Histone Deacetylase Inhibitor), IIinotecan (Topoisomerase Inhibitor)	14 days or 5 half-lives, whichever is longer

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

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

10.11. Appendix 11: 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
AKI	acute kidney injury
ALT	alanine aminotransferase
AMS	accelerator mass spectrometer
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the concentration-time curve over 24 hours
AUC_{inf}	area under the concentration-time curve to infinity
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
AUC_{tau}	area under the concentration-time curve at steady state over the dosing interval tau
AV	atrioventricular
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
BCS	Biopharmaceutics Classification System
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL	clearance
CL/F	apparent clearance of drug from plasma
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report

Abbreviation	Term
CT	clinical trial
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
dn	dose-normalized
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
F	absolute oral bioavailability
F_a	fraction of dose absorbed
FDA	Food and Drug Administration
F_g	fraction escaping gut metabolism
F_h	fraction escaping hepatic first-pass elimination
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure

Abbreviation	Term
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous(ly)
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block
LC/MS/MS	liquid chromatography tandem mass spectrometric method
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MEN2	multiple endocrine neoplasia type 2
MIST	Metabolites in Safety Testing
MQI	medically qualified individual
MRT	mean residence time
MTC	medullary thyroid carcinoma
NA	not applicable
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
OATP	organic anion transporting polypeptide
PD	protocol deviation
PE	physical exam
PK	pharmacokinetic(s)
PO	oral(ly)
PPI	proton pump inhibitor
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QP	qualified person
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
SAE	serious adverse event
SAI	site administration instructions

Abbreviation	Term
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SSID	study-specific participant identification
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	plasma elimination half life
T2DM	type 2 diabetes mellitus
TA	Technical Agreement
T bili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to reach C_{max}
UACR	urine albumin/creatinine ratio
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
UPLC-HRMS	ultra-high performance liquid chromatography coupled high resolution mass spectrometry
US	United States
V_{ss}	steady-state volume of distribution
V_z/F	apparent volume of distribution
WBA	whole body autoradiography
WBC	white blood cell
XTC	ecstasy

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